American Journal of Diseases of Children

VOLUME 57 MAY 1939 NUMBER 5

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VIRUS PNEUMONIA OF INFANTS SECONDARY TO EPIDEMIC INFECTIONS

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Morphologic diagnosis of a virus infection encountered in routine postmortem examinations would depend in general, if not always, on the recognition of specific cellular changes such as are now generally accepted as presumptive evidence of an infection of this nature. Especially significant would be the presence of cellular inclusions of certain types, cytoplasmic or nuclear or both. The inclusions of the cytoplasm are sometimes more characteristic of the particular virus concerned than are those which occur within nuclei, and in certain instances they are pathognomonic of the infecting agent. Although intranuclear inclusions are less characteristic of the specific virus, it is probable that they too are unique for each virus that causes them, notwithstanding one's inability to differentiate them accurately at present.

In the diagnosis of a virus infection one also takes into account the type or types of cells involved and the effect on them of the agent concerned, as well as the distribution and general character of the lesions.

Because of our interest in virus infections, we have for several years been on the lookout for evidences of the activity of these agents in our routine autopsies, especially in examinations of the respiratory tract, because it is well known that the respiratory system is affected in a number of virus diseases in man. In spite of rather careful observations, we have only relatively recently encountered evidence which could reasonably be interpreted as indicating the activity of a virus in the respiratory system, except in certain instances in the lungs of chil-

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dren, to be considered more in detail under the heading "Comment."[1] In these instances there were "protozoa-like cells" identical with those which appear not infrequently in the parotid glands of infants and of several species of lower animals and which, in the case of guinea pigs and mice, have been demonstrated to be caused by viruses.[2]

In the present paper we wish to record 5 cases of a specific type of respiratory infection in infants. The oldest infants affected were 2½ years of age. The lesions in the respiratory tract were such as to indicate that, notwithstanding associated bacterial infection, a specific virus determined the fairly distinctive phenomena encountered both grossly and macroscopically. Characteristic intranuclear inclusions, present almost exclusively in epithelial cells of the trachea and bronchi, of their mucous glands and of the alveoli, were an essential detail; epithelial necrosis, ulceration of the tracheal and bronchial mucosa and interstitial pneumonia followed, contributing a peculiar architecture to the lesions.

It is of especial interest that the first instance of this sort that we encountered occurred in 1931, following measles; in this case the effects of the virus infection were mild. The next case occurred in 1936 in an infant 2 weeks old who had no history of previous infection; the remaining 3 cases occurred in the early spring of 1938 during an epidemic of measles and whooping cough. In 2 of the 3 cases the condition followed measles, and in 1 clinical whooping cough. In the last case we were not able to cultivate Haemophilus pertussis from the lungs or to demonstrate lesions of whooping cough at autopsy.

Thus the virus infection to be described has been, in all but 1 instance, secondary either to measles (3 cases) or to whooping cough (1 case). The conclusion may be drawn that the incidence of this infection has increased in this territory in the last year or two, if so few cases may be taken as indicative samples. The infection is severe and can lead to fatal pneumonia in infants, if not primarily, at least by laying the foundation for bacterial invasion. All of the cases recorded have come from the central part of Tennessee.

In 1 typical instance the virus infection was recognized by means of frozen sections while fresh tissue was still available for animal

1. (*a*) Goodpasture, E. W., and Talbot, F. B.: Concerning the Nature of "Protozoa-Like" Cells in Certain Lesions of Infancy, Am. J. Dis. Child. **21**:415 (May) 1921. (*b*) Farber, S., and Wolbach, S. B.: Intranuclear and Cytoplasmic Inclusions ("Protozoa-Like Bodies") in the Salivary Glands and Other Organs of Infants, Am. J. Path. **8**:123, 1932.

2. Cole, R., and Kuttner, A. G.: A Filterable Virus Present in the Submaxillary Gland of Guinea Pigs, J. Exper. Med. **44**:855, 1926. McCordock, H. A., and Smith, M. G.: The Visceral Lesions Produced in Mice by the Salivary Gland Virus of Mice, ibid. **63**:303, 1936.

inoculation. Rabbits, mice and young opossums showed no evidence of infection after inoculation. A Macacus rhesus monkey, having received a suspension of infected lung intratracheally while under ether anesthesia, showed an elevation of temperature on the fourth day; this lasted about twenty-four hours, without clinical symptoms, and was followed by recovery.

REPORT OF CASES

CASE 1.—A 2½ year old boy was brought into the Vanderbilt University Hospital on Jan. 5, 1931, for diagnosis of his condition. The family history and past history were irrelevant.

Present Illness.—Three and one-half months previously the boy had aspirated a bean. By pounding him on the back the mother was able to get out a few small pieces. After this, the child seemed well until that night, when he began to breathe rapidly, but had no fever. The next day he refused his dinner, was feverish and vomited. For the next three or four weeks he had a chill and fever every other day. The fever was always preceded by a coughing spell. The boy failed to gain normally. One month after onset he began to have spells of coughing at night. Two and one-half months after onset he began to have night sweats. The fever ranged higher, and the patient became progressively sicker.

Physical Examination.—The patient was extremely sick, and the respirations were slow. The right lung was resonant throughout. The percussion note was dull over the entire posterior portion of the left lung. Anteriorly, there was an area of dull tympany just below and lateral to the nipple. This area was about 2 cm. in diameter, and the tissue around it was almost flat. A similar area was made out in the apex of the left lung. Many rales were heard over the entire left side of the chest. The breath sounds were diminished. The liver and spleen were both enlarged. There was marked clubbing of the fingers of both hands.

Roentgen Examination.—The diagnosis was multiple abscesses of the left lung.

Laboratory Examination.—The blood contained 4,000,000 red cells and 18,350 white cells per cubic millimeter. The hemoglobin content was 43 per cent. No parasites were seen. The Wassermann reaction was negative.

The urine had a specific gravity of 1.027; no albumin, cells or casts were noted. A blood culture was sterile. The tuberculin reaction was negative.

Course.—The patient was given several transfusions and showed some improvement during the first ten days in the hospital. Two weeks after admission he became much worse; the fever rose. At this time the breath was extremely foul, and the boy coughed up some foul-smelling sputum. He was placed in an oxygen tent. The temperature gradually fell to normal. After about two weeks the patient seemed improved. The transfusions were continued. Then there developed multiple subcutaneous abscesses, some of which were incised. Roentgen study showed some resolution of the consolidation at the base of the left lung, but the lung was still riddled with cavities. Measles developed on March 31, and the child was extremely sick for one week. After this, rales were heard at the base of the right lung. A hordeolum appeared on the right eyelid. After the attack of measles the patient lost ground steadily; he had a septic temperature, and three months after admission, on April 11, he died.

Clinical Diagnoses.—There were abscess of the lungs, multiple on the left; secondary anemia; undernutrition; pulmonary osteoarthropathy; bronchopneumonia; measles; multiple staphylococcic abscess of the skin, and hordeolum.

Anatomic Diagnoses.—These were: chronic bronchiectasis on the left; bronchopneumonia on the right; multiple abscesses of the lung, and acute enterocolitis.

Bacteriologic Examination.—A blood culture was negative; a mixed flora was obtained from the lungs.

CASE 2.—*Present Illness.*—A 2 week old boy was admitted to the pediatric service of the Vanderbilt University Hospital on Nov. 15, 1936. He was born at full term, weighing 7½ pounds (3,402 Gm.). He would not nurse, and there had been great difficulty in getting him to take a bottle, so that he was fed with a spoon and a nipple, receiving much less than the ordinary formula. The infant had not vomited or had diarrhea. Five days before admission he began to have frequent attacks of cyanosis without convulsion. He was admitted because of failure to nurse.

Physical Examination.—The temperature was 99 F. The patient was malnourished and dehydrated, weighing 5½ pounds (2,495 Gm.). The skin was extremely dry and loose, but there was no cyanosis. Several crusted areas were present about the umbilicus. The head was not abnormal in size or shape, but the fontanels were open, and the sutures were prominent. The tongue was covered with exudate, and the mucous membranes were slightly blue. The lungs were clear, and the heart was not enlarged and showed no murmurs. The abdomen was not abnormal. Both feet turned outward, but there was no impairment of motion. The reflexes were normal. There was marked clubbing of the feet.

Laboratory Examination.—There were 4,950,000 red blood cells per cubic millimeter, with 14.8 Gm. of hemoglobin per hundred cubic centimeters. There were 31,340 white cells per cubic millimeter, of which 77 per cent were neutrophils. The urine contained no albumin, red cells or casts. Sugar was present (1 or 2 plus). Examination of the stools gave negative results. Smears of material from the umbilicus showed typical myceliums.

Roentgen Examination.—On November 20 there was a small area of density in the lower portion of the upper lobe of the right lung, due to consolidation. There was an increase in the bronchovascular shadow, due to bronchitis. On November 23 the area of densitiy in the upper lobe of the right lung was a little less distinct; these findings were consistent with pneumonia which was undergoing resolution. On November 27 the area of density in the upper lobe of the right lung had extended into the extreme apex; it was apparently due to pneumonia. The lower portion of the upper lobe showed disappearance of the consolidation.

Course.—Shortly after admission the child began to have a temperature as high as 103 F. and diarrhea. The fever was thought to be due to dysentery and dehydration. On November 20 the diarrhea had subsided, but the fever was 101 F. The patient was cyanotic and appeared extremely ill. Examination of the chest revealed fine rales over the upper lobes of both lungs. The child was given oxygen intranasally and fluids. The illness ran a stormy course for the next few days, and there continued to be clinical evidence of bronchopneumonia. On November 23 the pneumonia was apparently resolving. The temperature dropped to 100 F., but the next day it was elevated to 103 F. and there was evidence of spread of the pneumonia. The patient was given two transfusions and prontosil (the disodium salt of 4-sulfamidophenyl-2″-azo-7′-acetylamino-1′-hydroxynaphthalene-3′,6′-disulfonic acid), but in spite of all measures there was progression of the pneumonia; death occurred on November 30.

Clinical Diagnoses.—These were bronchopneumonia; malnutrition; impetigo; thrush, and talipes equinovarus.

Anatomic Diagnoses.—These were bilateral confluent bronchopneumonia; staphylococcic abscess of the skin; focal necrosis of the liver, and petechial hemorrhages of the epicardium and spleen.

Bacteriologic Examination.—Culture of material from the lung yielded Haemophilus influenzae, Bacillus mucosus capsulatus and Streptococcus viridans. The pustules of the skin contained Staphylococcus aureus.

CASE 3.—*Present Illness.*—A 13 month old girl was admitted to the pediatric service of the Vanderbilt University Hospital on March 23, 1938, and died forty-five minutes after entrance. She had been in good health until five days previously, at which time she had fever, cough, coryza and a generalized rash. There had been exposure to measles. Three days before admission the rash began to fade, but on that date the respiration became grunting and rapid; the infant appeared cyanotic, and the temperature was 105 F. On the day of admission she had a generalized convulsion lasting five minutes.

Physical Examination.—The temperature was 103 F. on admission (it had been as high as 107 F. on the same day). The child appeared moribund; the mucous membranes were dry and deeply cyanotic. The respirations were rapid and shallow; the extremities, neck and vertebral column were held rigidly, and the child was having a clonic convulsion at the time of examination. The skin was dry and showed a fading coppery macular eruption, which was most marked on the lower extremities. The eyes, ears and throat were not examined. The chest was hyperresonant; the breath sounds were distant, and both lungs were full of fine moist rales. The heart could not be percussed; the rhythm was regular, the rate was rapid, and the sounds were distant. The abdomen was rigid and distended.

Course.—The child was taken immediately to the ward and placed in an oxygen tent. Gastric lavage was done, and a great amount of fluid was obtained. Fluids and calcium gluconate were given, but the child had a generalized convulsion, during which she died.

Clinical Diagnoses.—These were measles and postmeasles bronchopneumonia.

Anatomic Diagnoses.—These were bilateral bronchopneumonia; acute tracheobronchial lymphadenitis, and focal necrosis of the adrenal glands.

Bacteriologic Examination.—A blood culture was sterile.

CASE 4.—*Present Illness.*—A 2½ year old girl was admitted to the pediatric service of the Vanderbilt University Hospital on April 28, 1938. The child had been in good health since birth until ten days before admission, at which time measles developed. Associated with this was mild diarrhea. She did not appear to be acutely ill, and the course of the illness was satisfactory until four days prior to admission. At this time she had a rather severe cough, high fever and anorexia. She continued to exhibit high fever and cough throughout the four days.

Physical Examination.—The temperature was 103 F., the pulse rate 120 and the respiratory rate 40. The patient was cyanotic; the respirations were grunting, and the child appeared acutely and critically ill. The skin was dry, dirty, inelastic and cyanotic, but presented no rash of any type. There was no glandular enlargement. The right ear drum was red and bulging, the landmarks and the reflex on this side being obliterated. The left ear drum was gray and dull. The mouth was dirty and contained many crusted and ulcerated lesions. There was no rigidity

of the neck. Examination of the lungs showed many fine moist rales throughout, but there were no changes in the percussion note and breath sounds. The heart was not enlarged, and there were no murmurs or rubs. The abdomen was scaphoid, and there were no grossly enlarged viscera.

Laboratory Examination.—There were 4,460,000 red blood cells per cubic millimeter, with 11.5 Gm. hemoglobin per hundred cubic centimeters. There were 14,600 white cells, of which 91 per cent were neutrophils.

Course.—The child was extremely ill and was immediately placed in an oxygen tent. Fluid was supplied by clysis and intravenous drip. Myringotomy was done on the left, but no pus was obtained. In spite of these measures, the child became progressively worse; she died eighteen hours after admission.

Clinical Diagnoses.—These were postmeasles bronchopneumonia; purulent otitis media, and dehydration.

Anatomic Diagnoses.—These were bilateral confluent bronchopneumonia; multiple bronchiogenic abscesses of the lungs, and acute bronchial and mediastinal lymphadenitis.

Bacteriologic Examination.—The lungs contained Staph. aureus and Streptococcus haemolyticus.

CASE 5.—*Present Illness.*—A 16 month old boy was admitted to the pediatric service of the Vanderbilt University Hospital on May 4, 1938. He had had no previous illnesses, and his developmental history was normal. Three weeks prior to admission he started to cough in paroxysms without whooping. There had been several cases of pertussis in the neighborhood. The cough gradually grew worse; the child often turned blue during the paroxysms but never vomited. One week after onset of the cough the mother noted that the child's lower extremities were swollen and that the face was somewhat edematous. The local physician reported that there was no urinary abnormality, and the edema subsided. The child appeared to be getting along well until three days prior to admission, at which time he had a clonic and tonic convulsion lasting fifteen minutes. The following day five more convulsions were experienced, and from that time the convulsions occurred at frequent intervals. The child also had anorexia, vomiting and constipation and took little liquid during this time.

Physical Examination.—The patient was poorly developed and somewhat undernourished. He exhibited continuous generalized twitching movements of all the extremities. The head was turned to the right and the eyes to the left. There were numerous large fading splotches over the legs, some of which were reddish brown. The head was large, with prominent frontal and parietal bossing, but the fontanels were closed. Owing to the constant lateral nystagmus, the fundi could not be visualized. The ear drums were not abnormal. A purulent nasal discharge was present, and the throat was injected. The neck was not stiff, but the body in general was rigid. Numerous rhonchi and fine crackling rales were heard throughout both lungs, but the percussion note was resonant. The heart was not enlarged; there were no murmurs or rubs, and the rate was rapid. Brudzinski's sign was present; the Kernig, Trousseau and Chvostek signs were absent. Clonus could not be demonstrated because of marked spasticity. There was slight pitting edema over the feet.

Laboratory Examination.—The blood contained 3,940,000 red cells per cubic millimeter, with 9 Gm. of hemoglobin per hundred cubic centimeters. There were 56,200 white cells, of which 72 per cent were neutrophils. The urine contained

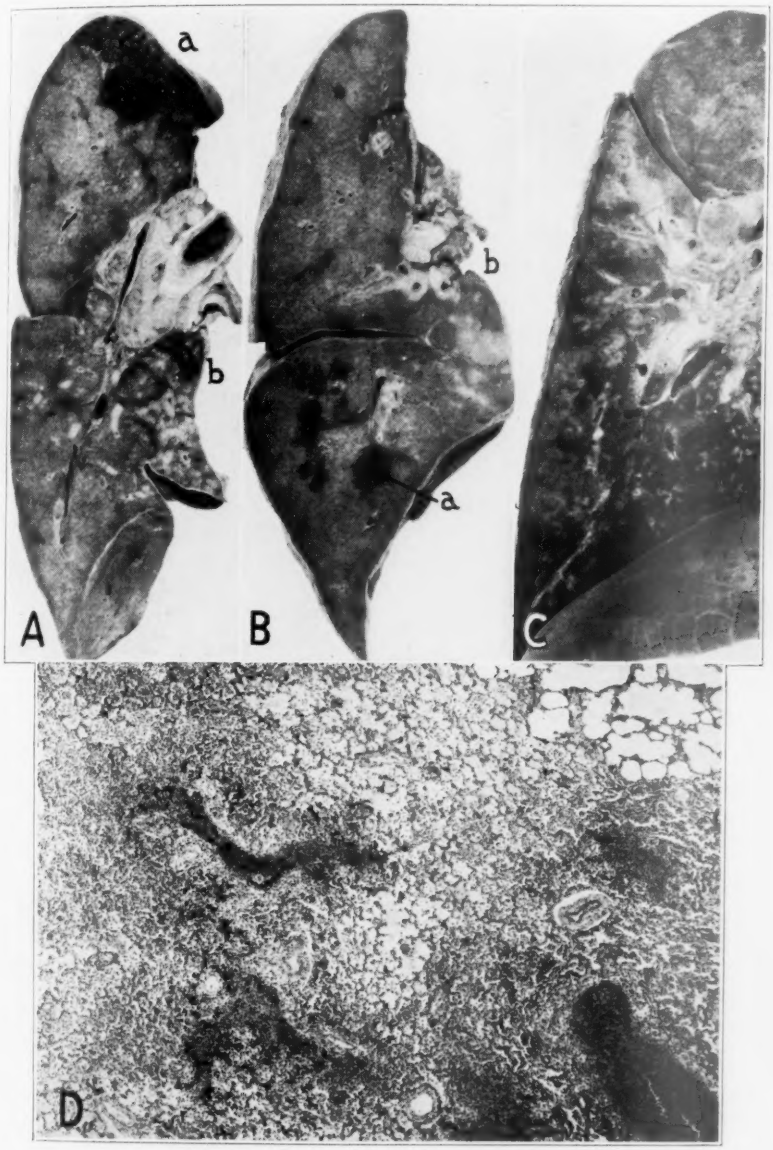

Fig. 1.—*A* (case 3), section of lung showing postmeasles pneumonia. Note hemorrhage (*a*) and areas of bronchopneumonia (*b*). *B* (case 4), postmeasles pneumonia. Note hemorrhages (*a*) and areas of bronchopneumonia (*b*). *C* (case 5), postpertussis pneumonia. Note extensive bronchopneumonia. *D*, characteristic low power view of an area of pneumonia with bronchial destruction, ulceration of bronchial mucosa and alveolar exudate. Magnification, approximately × 26.

albumin (2 plus) and sugar (2 plus) but otherwise appeared normal. The serum contained 9.5 mg. of calcium and 5.3 mg. of inorganic phosphorus per hundred cubic centimeters. The Kahn reaction was negative.

Roentgen Examination.—On May 17 there was rather diffuse bronchopneumonia in both lungs, probably little more marked on the left than on the right.

Course.—The temperature on admission was 103 F. During the first fifteen hours after admission the child had five convulsions. He showed very rapid respiration, with the Cheyne-Stokes type of breathing. A lumbar puncture was done, and the convulsions became less frequent and the spasticity less marked. The only sign of abnormality in the spinal fluid was a 2 plus Pandy reaction. After this the child was given calcium gluconate and dextrose intravenously This appeared to quiet him somewhat. The following day the temperature was 105 F.; the respirations were more labored, and there were almost continuous convulsions of the left side of the body. The boy was placed in an oxygen tent and other measures were instituted, but he died that day.

Clinical Diagnoses.—These were pertussis; acute encephalitis due to H. pertussis; bronchopneumonia, and rickets.

Anatomic Diagnoses.—These were bilateral confluent bronchopneumonia; focal necrosis of the liver and spleen; focal hemorrhages of the brain, and acute bronchial and mediastinal lymphadenitis.

Bacteriologic Examination.—A blood culture yielded an unidentified gram-negative bacillus. From the lungs were obtained pneumococcus and a gram-negative bacillus (not H. pertussis).

GROSS LESIONS OF THE RESPIRATORY TRACT

Because the respiratory tract in these 5 cases presented a fairly uniform picture, a composite description will be given rather than the detailed observations in each case. No other system or organ in any case presented lesions of considerable importance or any which had an evident bearing on the infection of the respiratory tract under consideration.

It is of interest that when a parotid gland in case 1 was examined histologically no protozoa-like cells were observed. In case 5, in which the condition followed clinical whooping cough, with signs and symptoms of pertussis encephalitis, the brain showed no histologic evidences of inflammation. The blood vessels were congested, and here and there were perivascular extravasations of erythrocytes. These were noted about both veins and arteries. No virus inclusions were observed in any cells of the nervous system.

Grossly in each case the trachea and the bronchi showed hyperemia, and their mucosas were dulled and thin, suggesting ulceration in places. Considerable stringy mucoid material was present within the lumens. The pleural cavities contained no excess of fluid, and the surfaces were smooth and glistening.

Superficially the lungs were variable as to evidences of consolidation. In case 4, however, the upper portion of the upper lobe of the right

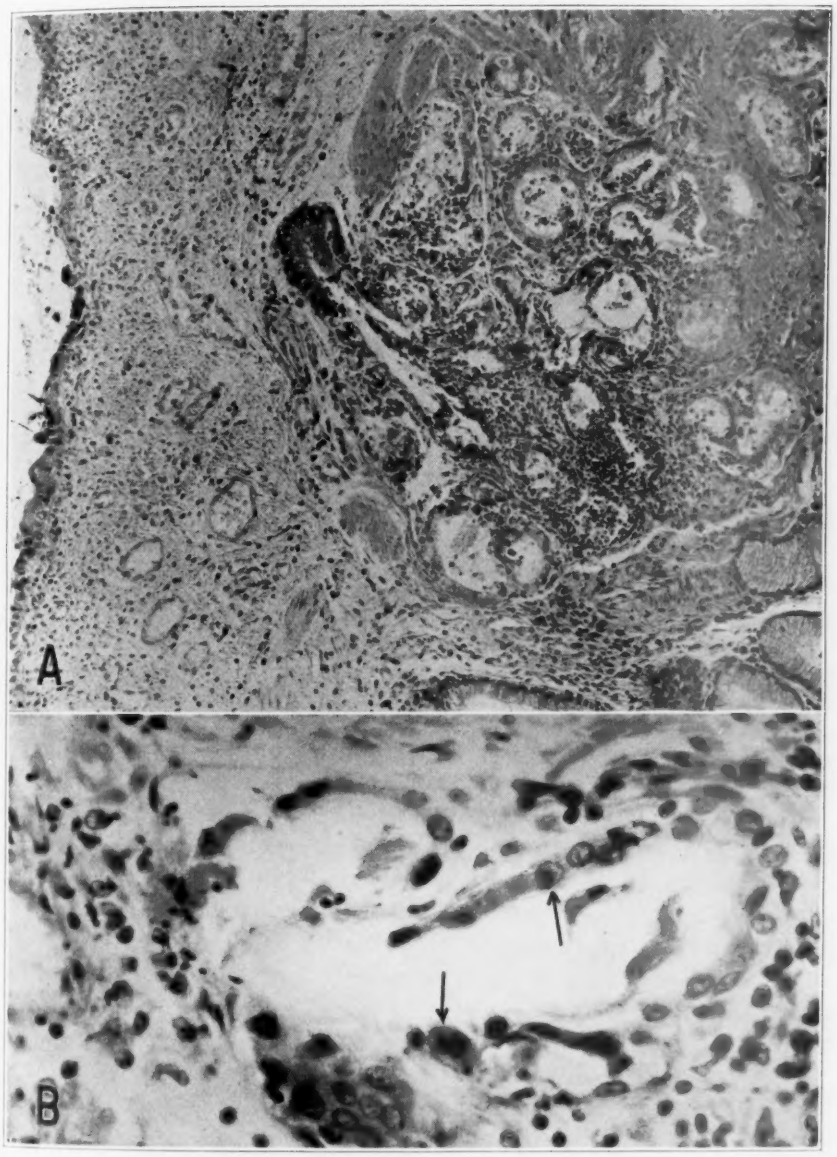

Fig. 2 (case 5).—*A*, section of a large bronchus, showing ulceration of mucosa and virus infection with necrosis of a mucous gland. Magnification, approximately × 270. *B*, acinus of a mucous gland of a bronchus, showing intranuclear inclusions and (left) necrosis of epithelium. Magnification, approximately × 435.

lung and the upper portion of the upper and the lower lobes of the left showed consolidation and a deep hemorrhagic appearance. In this case small subpleural foci of atelectasis were observed in each lobe. Elsewhere the lungs were expanded and crepitant.

When the lungs in each case were sectioned, scattered areas of consolidation were observed. In 2 instances such areas were most conspicuous near the hilus in the lower lobes. One of the most characteristic features was the presence of hemorrhage in the lung, isolated or situated about areas of definite inflammatory consolidation.

A particular feature of the consolidated areas was their relation to bronchi and bronchioles. In the center of each of these areas was a softened, opaque spot or line, variable in size and consisting of pus surrounded by a thin zone of pneumonic consolidation which often was red itself or was encircled by a zone of hemorrhage. The central areas had the gross appearance of small bronchiectatic abscesses or of bronchi and bronchioles filled with exudate. In case 1 the gross appearances were greatly modified by the presence of extensive chronic bronchiectasis of the left lung following the aspiration of a bean; in case 5 the bronchiolar lesions were much more extensive than in any other case and resembled those caused by H. influenzae.[3]

MICROSCOPIC LESIONS OF THE RESPIRATORY TRACT

In each case the trachea and the larger bronchi presented similar changes. The surface was completely denuded of ciliated epithelium and was in part ulcerated. The remaining surface was covered by a thin epithelial membrane, often only one cell thick. The ulcerated areas were sometimes covered by fibrin. There were scattered areas of necrosis in the mucous glands, involving one or more lobules. This was one of the most characteristic features of the process.

Just beneath the basement membrane of the mucosa there was an exudate of polymorphonuclear leukocytes, especially abundant at areas of ulceration; in other places it was admixed with mononuclear cells of various sorts. Polymorphonuclear leukocytes were present in and on the epithelial layer.

The smaller bronchi and bronchioles frequently showed complete destruction of epithelium. The lumens were filled with cellular exudate and necrotic débris, and frequently bacteria could be demonstrated in them. The lumens were distended with leukocytes and were surrounded by inflammatory exudate.

Extending beyond and about the bronchioles were patches of pneumonitis involving alveoli. The exudate varied in composition. At

3. Brannan, D., and Goodpasture, E. W.: The Pathology of Pneumonia Caused by Bacillus Influenzae During an Inter-Epidemic Period, Arch. Int. Med. **34**:739 (Dec.) 1924.

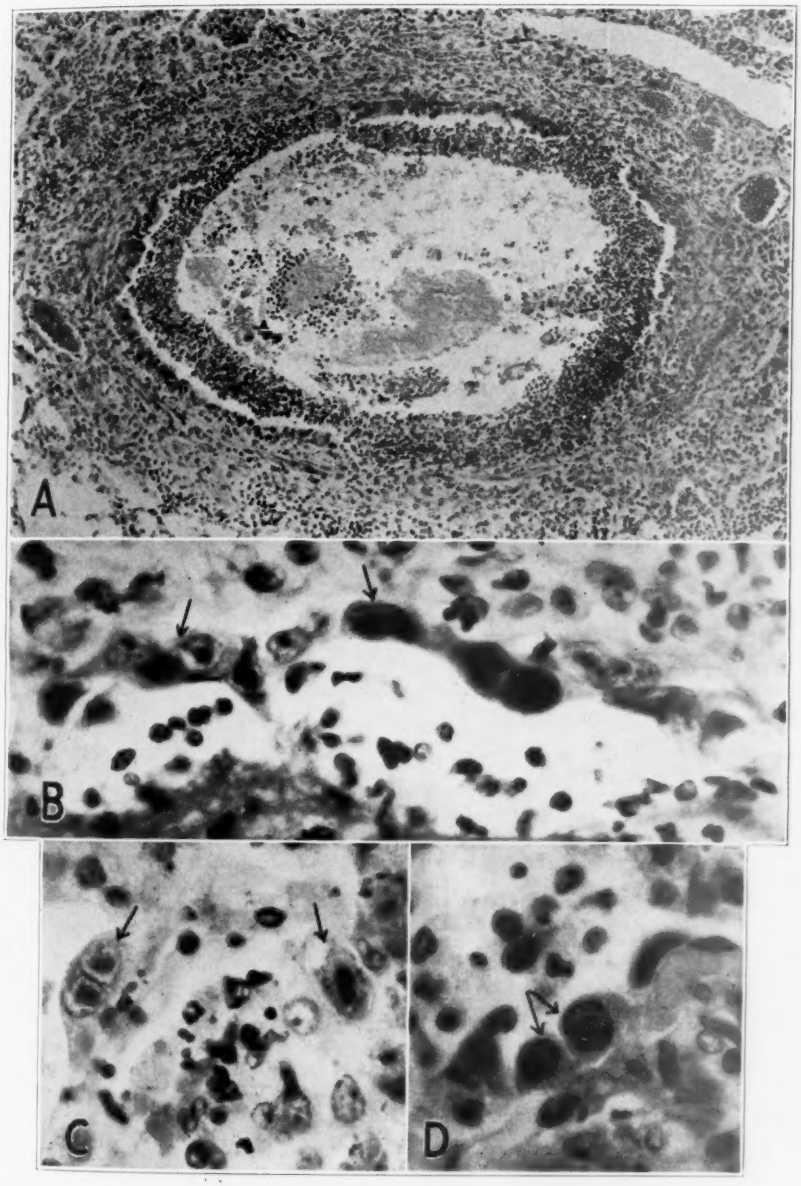

Fig. 3.—*A*, bronchus showing ulceration and leukocytic exudate. Magnification, approximately × 90. *B*, tracheal mucosa with a single layer of epithelial cells, most of which contain intranuclear inclusions. Magnification, approximately × 600. *C* (case 5) and *D* (case 2), intranuclear inclusions in alveolar epithelial cells. Magnification, approximately × 565 and × 750, respectively.

times it was predominantly hemorrhagic, and in places it was fibrinous and cellular. Polymorphonuclear cells and monocytes were the chief cellular elements, although other mononuclear cells were usually present. In the neighborhood of alveolar ducts the alveolar and ductular exudate was extremely compact, and there was much fragmentation of nuclei. This gave a rather characteristic appearance which suggested the early lesions of tularemia. Alveolar walls were involved in the necrotizing process, which extended outward from the bronchioles. Bacteria could be demonstrated in the lumens of bronchioles and in the areas of necrosis.

CELLULAR INCLUSIONS

The specific feature of the process was the presence of intranuclear inclusions, which were almost entirely restricted to epithelial cells. In 1 instance a few fibroblasts surrounding an ulcerated bronchus contained similar, though smaller, bodies within their nuclei. No cytoplasmic inclusions were observed.

The specific nuclear inclusions were slightly acidophilic structures, granular but compact, situated within the nucleoplasm and separated from the nuclear membrane by a clear zone which either appeared empty or was traversed by delicate strands which were radially disposed and connected the inclusion with the nuclear membrane. Sometimes the inclusion filled the nucleus, and then, like similar inclusions in cases of herpes simplex, it appeared to be slightly basophilic and finely granular. Often nucleoli could be distinguished from the adjacent inclusion.

The affected nuclei, and often the entire cell, were slightly enlarged, but not to so great an extent as were the cells affected by the parotid virus. Furthermore, the involved cells rapidly underwent necrosis, and this was the essential cause of the extensive ulceration.

Many such inclusions were noted in the epithelial cells of the trachea and bronchi, within the epithelial cells of their mucous glands and within alveolar epithelium.

EXPERIMENTAL INOCULATIONS

The virus infection in the lung in case 5 was recognized by observing the characteristic intranuclear inclusions in frozen sections while the lung was still fresh. Because the cellular changes were suggestive of an infection with the herpes simplex virus, 2 rabbits were anesthetized, and ground lung was rubbed into a scarified cornea of each animal. The corneas healed within twenty-four hours, and no evidence of herpetic keratitis or of any other infection developed. All the experiments to be described were performed while the animals were anesthetized with ether.

Three rabbits received by intracerebral injection 1 cc. each of a Berkefeld V filtrate of a 20 per cent suspension of ground lung in a 0.9 per cent solution of sodium chloride. These animals remained normal. An unfiltered 20 per cent suspension of ground lung in a 0.9 per cent solution of sodium chloride was dropped into the noses of 7 white mice, 2 rabbits and 2 young opossums. None of these animals showed any evidences of disease. Three tenths of a cubic centimeter of a similar emulsion was injected into a testis of each of 2 adult rabbits. A nonspecific, nontransmissible lesion occurred. One cubic centimeter of the suspension was injected intratracheally into 2 rabbits. Both remained normal. The same amount was injected intratracheally into a young Macacus rhesus monkey. On the fourth day this animal had a slight febrile reaction that lasted for twenty-four hours. No other symptoms appeared. Lung emulsion placed on the chorioallantoic membrane of incubating hen's eggs killed the embryos by bacterial infection. Lung filtrate induced no specific lesion.

We were thus unable to induce infection with fresh lung tissue, but we believe that these experiments eliminate herpes simplex virus as the cause of the cellular changes observed.

COMMENT

The question arises as to whether or not the specific cellular changes observed in our cases can be distinguished from those which are known to have occurred in the lungs and in other organs of infants who have died of whooping cough and other diseases. The protozoa-like cells of this so-called inclusion disease of infants were first described in 1904 by Jesionek and Kiolemenoglou.[4] They were concluded to be amebas by Smith and Weidman,[5] but were shown to be modified human cells by Goodpasture and Talbot [1a] in 1921. Since then they have been described by numerous observers, whose papers were reviewed by Farber and Wolbach.[1b]

Because of the relatively frequent occurrence of these cells in association with pertussis, it has been suggested by McCordock and Smith [6] and by Rich [7] that they might indicate an initial virus infection

4. Jesionek and Kiolemenoglou: Ueber einen Befund von protozoënartigen Gebilden in den Organen eines hereditärluetischen Fötus, München. med. Wchnschr. **51**:1905, 1904.

5. Smith, A. J., and Weidman, F. D.: Infection of a Stillborn Infant by an Amebiform Protozoön (Entamoeba Mortinatalium, N. S.), Univ. Pennsylvania M. Bull. **23**:285, 1910.

6. McCordock, H. A., and Smith, M. G.: Intranuclear Inclusions: Incidence and Possible Significance in Whooping Cough and in a Variety of Other Conditions, Am. J. Dis. Child. **47**:771 (April) 1934.

7. Rich, A. R.: On the Etiology and Pathogenesis of Whooping Cough, Bull. Johns Hopkins Hosp. **51**:5, 1932.

as a precursor to whooping cough. Because of their absence in the majority of cases of pertussis and their occurrence in association with a variety of other conditions, there does not seem to be a good reason for accepting this hypothesis.

Such a lesion differs in several respects from that noted in the 5 cases we are reporting. In the first place, the cells in the "inclusion disease" characteristically become exceedingly large whether they are epithelial or mesodermal in origin; the affected mesodermal cells in their characteristic form are indistinguishable from those of epithelial origin, but they at least are actively ameboid, penetrating blood capillaries and becoming distributed to several organs, including the kidneys, the adrenals and the liver. The virus of this condition affects likewise epithelial cells of the parotid ducts and of the convoluted tubules of the kidney. Rarely does one find these cells in a necrotic state, and the infection seems to be chronic and to cause little or no damage to the host.

Although the affected epithelial cells of the respiratory tract in the 5 cases under discussion were frequently somewhat enlarged, they were not seen to resemble in this respect those of the "inclusion disease." They were not observed in any organ or tissue other than the respiratory tract; the involved tissues were severely damaged. The inclusions themselves were in general less compact and not as large as those of "inclusion disease," and in no instance were associated cytoplasmic inclusions observed.

We are of the opinion, therefore, that the virus responsible for the changes in our 5 cases is different both from that of herpes simplex and from the active agent of so-called inclusion disease. If it is related to the latter, it must be an unusually virulent strain which has become altered in such a way as to cause a different sort of lesion. Our data being purely morphologic, we have no evidence at present of its nature in other respects.

Since there are indications that this virus infection is becoming increasingly important as a secondary invader of the respiratory tract after acute epidemic diseases of this area, tending to initiate fatal bacterial invasion of the lungs, it seems important for pathologists to be on the lookout for it and, if possible, to find a suitable experimental host for its closer study.

SUMMARY AND CONCLUSIONS

Five cases of a hitherto undescribed virus infection of the lungs of infants, especially following measles and whooping cough, have been observed and recorded.

The virus invasion usually appeared to be secondary and tended to pave the way for bacterial infection of the lungs.

The presence of the virus was indicated by the occurrence of nuclear inclusions in epithelial cells of the trachea and bronchi and their mucous glands and of the alveolar epithelium. Rapid necrosis of the affected cells occurred, resulting in ulceration of surfaces.

The virus appeared to be different from that of herpes simplex and from the agent of the so-called inclusion disease of infants.

Experimental inoculation of infected lung tissue into rabbits, mice, opossums, chicken embryos and a Macacus rhesus monkey failed to establish the infection.

CLOSE SUCCESSION OF CASES OF ERYTHEMA NODOSUM OF NONTUBERCULOUS PATHOGENESIS

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That erythema nodosum, as a rule, is a tuberculous symptom complex is undoubted. This has been indicated by previous observations. Decisive evidence of it was given in the investigation described by one of us (H. E.[1]) at the first Northern Congress for Pediatrics, held in Copenhagen in 1919, and later presented in a more explicit form. In a number of cases of erythema nodosum it was demonstrated not only that all the patients reacted positively to tuberculin but that the source of the symptom complex lay in a tuberculous focus. In the greater number of cases this focus was localized in the bronchial glands and the lungs. Exceptionally there was localization in another region, such as the cervical lymph nodes. The investigations just mentioned threw a fresh light on a pathologic picture which until then had been obscure.

Some earlier investigations (especially Pollak's[2] tuberculin tests in a number of cases studied at an outpatient department) pointed to the probability of a connection between tuberculosis and erythema nodosum. But as in such cases the tuberculous disease—or rather the tuberculous focus—which was the source of the erythema had not been found, it was natural that a negative attitude, in general, was taken toward the assumption of a tuberculous cause. Contributing to this skepticism were the fruitless attempts to demonstrate the presence of tubercle bacilli in the efflorescences of erythema nodosum. The application of the phrase "no tuberculosis without tubercle bacilli" (Lewandovsky) to the disease called erythema nodosum was entirely natural at that time.

It was subsequently proved by Ernberg's investigations that a tuberculous disease undoubtedly existed in the cases investigated. The skin was the seat of the characteristic alterations visible to the eye but not of the essential morbid process. What, then, could be the explanation

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From the Sachs Children's Hospital.

1. Ernberg, H.: (*a*) Jahrb. f. Kinderh. **95**:1, 1921; (*b*) Erythema Nodosum and Tuberculosis, Am. J. Dis. Child. **46**:1297 (Dec.) 1933; (*c*) Svenska för. f. inv. med. förhandl., 1930, p. 171.

2. Pollak, R.: Wien. klin. Wchnschr. **25**:1223, 1912.

of the efflorescences in the skin? On the basis of further investigations, Ernberg made the deduction that the syndrome must be an expression of an autogenous reaction of the organism to tuberculin. In other words, the efflorescences were symptomatic of an anaphylactic or, more properly, of an allergic process of tuberculous origin.

As increasing interest was taken in the disease and as in every concrete case the tuberculous causation was probable, tuberculin tests in these instances became usual. Gradually, however, came news of patients with erythema nodosum who reacted negatively to tuberculin. How was this to be interpreted?

As is known, the tuberculin reaction in cases of erythema nodosum is not always but usually severe, even with such a small amount of tuberculin as that employed in a Pirquet or some other cutaneous test. It would of course be strange if a patient with erythema nodosum of tuberculous origin should react negatively to a tuberculin test with larger doses, carried out according to rule.

Koch,[3] like Ernberg, pointed out the possibility that simultaneously with the existence of the symptom complex of erythema nodosum there might arise a deficient or a weak reaction to tuberculin. Ernberg [1c] has developed this theory in more detail.

As we have said, however, there came an increasing number of communications from Sweden and from other countries concerning cases of erythema nodosum in which the reaction was negative, even after large doses of tuberculin, and remained negative, in some instances for months or years (Johannsen;[4] Landorf;[5] Malmberg;[6] Lichtenstein;[7] Wallgren,[8] and others). At the Sachs Children's Hospital also such cases have been observed.

It is remarkable that in none of these cases have tubercle bacilli been found in the ventricular lavage fluid. It must also be noted that as a rule no hilar-alteration—at least none of any considerable degree—could be demonstrated by roentgen study in these cases.

These observations made it increasingly probable that besides cases of tuberculous erythema nodosum there exist cases in which there is another cause.

According to various reports made by Swedish investigators, the frequency of cases of erythema nodosum in which the tuberculin reaction is negative has hitherto varied between 0 and 8 per cent.

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3. Koch, H.: Extrapulm. Tuberk. **1**:22, 1926.
4. Johannsen, N.: Acta pædiat. (supp. 1) **17**:218, 1935.
5. Landorf, N.: Acta pædiat. (supp. 1) **17**:180, 1935.
6. Malmberg: Acta pædiat. (supp. 1) **17**:223, 1935.
7. Lichtenstein: Acta pædiat. (supp. 1) **17**:219, 1935.
8. Wallgren, A., in Engel, S., and von Pirquet, C.: Handbuch der Kindertuberkulose, Leipzig, Georg Thieme, 1929-1930.

During the spring of 1937, there was in Stockholm a remarkable and strangely frequent occurrence of cases in which the tuberculin reaction was negative, a circumstance of great interest, both from a theoretic and from a practical point of view.

During two months in the spring of 1937 there were admitted to the Sachs Children's Hospital 6 patients with erythema nodosum, none of whom reacted to tuberculin given in large doses. As during the preceding ten years we had observed in this hospital only 4 patients with erythema nodosum who reacted negatively, the new state of affairs was remarkable. With the cooperation of the chief physicians at the three other children's hospitals in Stockholm, Drs. Lichtenstein, Malmberg and Wernstedt, we were able to gain an idea of conditions throughout the city as a whole. The report concerns only the inmates of the children's hospitals.

Incidence of Erythema Nodosum in the Children's Hospitals of Stockholm

Year	Tuberculin Reaction	
	Positive	Negative
1928	64	1
1929	37	6
1930	40	3
1931	34	1
1932	45	4
1933	44	3
1934	48	4
1935	30	5
1936	44	7
Total	386	34
1937*	14	20

* The figures for 1937 cover only the months from January to June, inclusive.

As for the diagnosis, we consider that this has been fully reliable in every case.

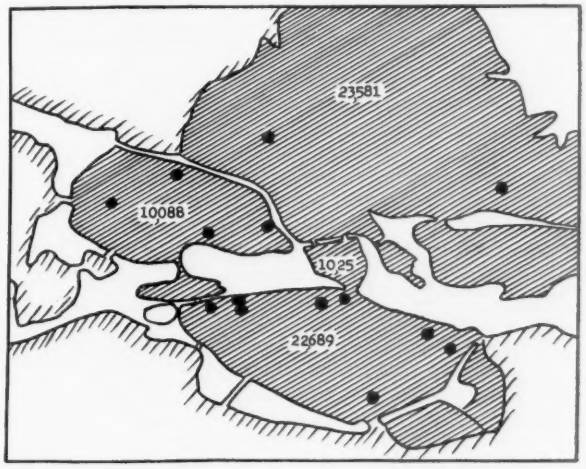
The table shows the number of children with erythema nodosum in all the children's hospitals of Stockholm since 1928.

Consequently, during the years 1928 to 1936 inclusive there were in the hospitals for children 420 patients with erythema nodosum, of whom 34, or 8.09 per cent, reacted negatively to tuberculin.

During the first six months of 1937 in all the children's hospitals 34 patients were treated for erythema nodosum. Of this number, 20 reacted negatively to tuberculin and only 14 positively. In other words, during this period the patients who reacted negatively were more numerous than those who reacted positively. That is in contrast to previous observations. As far as we are aware, such a concentration of cases of erythema nodosum in which the tuberculin reaction was negative has never before been described.

It is remarkable that in all the cases in which reactions were negative the condition occurred within a limited period, viz., during April and May, while in all the cases in which it was positive occurrence was fairly equally spread over the period from January to June inclusive. In addition, on investigating the distribution of the patients we discovered a regional irregularity of incidence in the town.

The dots on the schematic map show the incidence of cases in which the tuberculin reaction was negative. Of the 14 patients in Stockholm, exclusive of the suburbs, 12 lived in the southern and western parts of the town. There was only 1 patient in Norrmalm and 1 in Östermalm, i. e., in the northern and eastern quarters of Stockholm. (On the map is indicated the number of children below 15 years of



Map of Stockholm, exclusive of suburbs, showing incidence of cases of erythema nodosum in which the tuberculin reaction was negative. The figures indicate the numbers of children under 15 years of age in the various sections of the city. The black circles represent children with the disease.

age who lived in different parts of the city.) Of the other 6 patients, 1 lived in a neighboring community south of Stockholm and the remaining 5 in western or southern suburbs of the town.

Possibly this is an expression of a regional concentration, but the material is not extensive enough to allow us to draw conclusions concerning this.

With regard to these 20 patients, we were able, of course, to observe the 6 who were admitted to the Sachs Children's Hospital during the period mentioned. Of the others, we had an opportunity to study 7 in detail.

Data on age and sex revealed no remarkable facts. The youngest child was 1 year and 5 months old and the oldest 12 years; most of the patients were between 3 and 5 years. There were 11 boys and 9 girls.

In the anamnesis we observed with the most careful attention any possibility of a disposition to tuberculosis or of exposure to the disease.

In 1 case one of the parents had had pleurisy in 1929, which at the time of the child's admission to the hospital was considered as healed. In none of the other 12 cases were the parents or brothers and sisters known to have had tuberculosis (in some cases it had occurred in such a distant relative as a maternal or paternal aunt). Exposure to tuberculosis could be assumed to have taken place in 2 cases occurring four and twelve months, respectively, before the outbreak of the erythema nodosum. Consequently, in no case was there noted the exposure to tuberculosis in close connection with the outbreak of erythema nodosum which is often found in cases of erythema nodosum of undoubtedly tuberculous pathogenesis.

The tuberculin testing in every case was begun with a Pirquet test and continued with increasing intracutaneous doses. In 1 case, the amount of tuberculin was increased to 1 mg.; in 6 cases, to 3 mg.; in 1 case, to 5 mg.; in 2 cases, to 10 mg., and in 3 cases, to 20 mg. In some instances, with the large doses of tuberculin moderate reactions were obtained; these were considered as pseudoreactions. In the other cases altogether negative results were obtained. In most of the cases, the testing was begun during the first week after the breaking out of the erythema and was ended, at the latest, during the third week. In 3 cases, a Mantoux test with 1 mg. was repeated after six, thirteen and twenty-one weeks, respectively, with negative results.

Roentgen investigation was carried out in all cases. In 8 instances the result was completely negative. In 4 cases a slight lymphoma was observed in the hilus. In 1 of these cases, there was also an interlobular streak on the left. Finally, in 1 case there was an increased central shadow in each pulmonary field. In some of the cases, therefore, roentgen study revealed small demonstrable alterations, but these were so slight in extent and character that it is impossible to make any deductions respecting them. In no instance were there observed such characteristic hilar alterations as are common in cases of erythema nodosum of demonstrably tuberculous nature. The ventricular lavage fluid was examined by the guinea pig test four times for 3 patients, six, nine, sixteen and twenty-one days, respectively, after the appearance of the erythema, but with a negative result in every case.

In 1 case (case 5), in which death occurred and which will be described later, the guinea pig test was made with an excised cervical

gland and on postmortem examination with a hilar and a mesenteric gland as well, also with negative results.

The rise in temperature in most cases lasted one to two weeks and remained within moderate limits (38 to 39 C. [102.2 to 104 F.]). In 1 case the whole course was without fever; in another case the temperature was 38.9 C. (102 F.) on one occasion, two days before the outbreak of the erythema, the remainder of the course being free from fever. One patient (case 5), who had septic adenitis, otitis, pneumonia and empyema, had fever of long duration and finally died. After the fading away of the erythema, in no case was there fever which could not be explained as the result of septic processes.

The sedimentation rate was high throughout. During the first week after the appearance of the efflorescence, the index (microsedimentation rate according to Ström[9]) lay between 40 and 50, corresponding to Westergren's values of 45 and 60. In the case in which there was no fever the rate was high (46).

REPORT OF CASES

CASE 1.—K. K., a girl aged 3 years and 3 months, was an inmate of the Sachs Children's Hospital from April 14 to May 5, 1937, because of erythema nodosum.

Her parents were healthy. A half-brother and a half-sister on the mother's side probably had tuberculosis at that time. The child herself had had measles.

The present illness began with fretfulness and a poor appetite, which lasted for two weeks. On repeated taking of the temperature there was no fever. On April 13 tender exanthems appeared on the legs.

Examination on the patient's admission to the hospital showed that the general condition was good. A typical exanthem was present on the anterior surfaces of the lower parts of the legs. The lungs, heart, abdomen and other internal organs were normal. Two glands as large as peas were palpable on the neck. The pharynx was slightly reddened. The temperature was 37.4 C. (99.3 F.).

The urine was normal. The Mantoux test, with up to 20 mg. of tuberculin, gave a negative reaction. The sedimentation index was 46 on April 14 and 19 on May 3.

During the whole stay in the hospital the patient was afebrile, except for a slight increase of temperature during a few days when she had pharyngitis, beginning on April 21. Roentgen study of the lungs made on April 21 elicited no comment. The girl was discharged, free from symptoms, on May 7. September 7 she was still free of symptoms, with a normal sedimentation rate and a negative reaction to the Mantoux test with 1 mg.

A 3 year old girl, somewhat listless for a fortnight, displayed typical erythema nodosum. She had a negative tuberculin reaction and appeared normal on roentgen study. She was free from fever with the exception of an elevation during some days of acute pharyngitis. It is remarkable that the sedimentation rate, even at the beginning of the erythema, was so high.

9. Ström, J.: Acta pædiat. **14**:567, 1933.

In the next case fever occurred before the outbreak of the erythema.

CASE 2.—E. F., a girl 1 year and 8 months old, was an inmate of the Crown Princess Louisa's Hospital from April 26 to May 5, 1937.

The mother had had erythema nodosum in 1935, when the lungs were examined and considered healthy. The eldest sister, aged 6 years, had had erythema nodosum when 3 years old, regaining health after ten days. The patient had varicella in January 1937, after which she was somewhat listless and tired. She had fever for three days a month before the present illness. Otherwise she had been healthy.

The present illness began on April 19 with fever (38.1 C. [100.6 F.]). Since then the child had been in bed at home with an evening temperature of over 38 C. (100.4 F.) for the first few days; afterward she was subfebrile. On April 24 erythema appeared on the lower parts of the legs. The patient ate and slept well. There was neither cold in the head nor cough.

On the patient's admission to the hospital she was in good condition but pale. On the lower parts of the legs were typical efflorescences of erythema nodosum. The heart and lungs were normal. The pharynx was slightly reddened and swollen. The sedimentation index was 45. The white blood cells numbered 13,600, of which nonsegmentated neutrophils comprised 2⅓ per cent; segmentated neutrophils, 54⅓ per cent; lymphocytes, 41⅓ per cent, and monocytes, 1⅔ per cent. The reaction was negative to as much as 3 mg. of tuberculin. In a roentgenogram of the lung the diaphragm and the sinus appeared normal. There was a somewhat increased central shadow in the pulmonary field, particularly on the right and at the base on the left. There was no reliable evidence of alterations in the parenchyma.

The patient was free from fever during the entire time at the hospital, with the exception of three days, beginning with April 30, when a rise of temperature was associated with acute pharyngitis.

A girl aged 1 year and 8 months, whose mother and sister had had erythema nodosum some years before, had fever (about 38 C. [100.4 F.]). On the sixth day of the illness she showed typical efflorescences of erythema nodosum and symptoms of a typical infection of the throat. The Mantoux reaction was negative to as much as 3 mg. of tuberculin.

In the next case erythema nodosum was associated with scarlet fever.

CASE 3.—R. D., a boy 8 years and 10 months old, was an inmate of the Crown Princess Louisa's Hospital from May 8 to 11, 1937, because of scarlatina and erythema nodosum.

The family history revealed no tuberculosis, and the child was not known to have been exposed to it. He had measles, parotitis and pertussis in 1936 but otherwise had been healthy.

On April 22 the boy had fatigue, pain in the throat and fever (40 C. [104 F.]). The temperature remained high for two days, after which it fell to 38 or 39 C. (100.4 or 102.2 F.). About April 25 large areas of prickly erythema appeared on the face and body. After April 30 the temperature rose. From the beginning there had been tenderness and adenitis of the cervical glands. On May 3 erythema was present on the legs. There had been a slight cold in the head and a cough during the few days before the boy's entry to the hospital.

On admission the general condition was good. On the legs were typical efflorescences of erythema nodosum. The lungs appeared normal. There was

a weak blowing systolic murmur above the pulmonary artery. The abdomen was normal. On each side of the throat was a row of fairly soft, tender glands, some as large as a hazelnut. The occipital glands were as large as grains of rice. The tonsils and pharynx were reddened. The temperature was 40 C. (104 F.). The sedimentation rate was 65. The white blood cells numbered 8,600. Of these, nonsegmentated neutrophils comprised 7 per cent; segmentated neutrophils, 52 per cent; eosinophils, ⅔ per cent; lymphocytes, 36⅔ per cent; monocytes, ⅔ per cent, and plasma cells, 2 per cent. The urine showed albumin (1 plus), with masses of red blood cells and casts.

The day after admission there appeared desquamation typical of scarlatina on the soles of the feet; so the patient was transferred to the Hospital for Epidemic Diseases. According to reports from this institution, the Mantoux reaction to 3 mg. was negative, and roentgen study of the lungs showed a normal condition.

There have been described many cases of erythema nodosum associated with scarlatina, including some in which the tuberculin reaction was negative. For instance, Moro [9] described a case of his own and referred to those previously known; he showed that the efflorescences of erythema nodosum usually appear between the third and the fourth week of the disease. In this case it appeared at the close of the second week.

Following are cases of 2 brothers who became ill with erythema nodosum in rapid succession.

Case 4.—T. E., a boy 4 years and 8 months old, was an inmate of the Sachs Children's Hospital from April 13 to 24, 1937, for erythema nodosum, suppurative bilateral otitis media, cervical lymphadenitis, and acute rhinopharyngitis, and from May 5 to 10 for acute pneumonia and empyema on the right with suppurative otitis media on the left.

The family history revealed no tuberculosis, and the child was not known to have been exposed to it. He had previously been healthy.

In the middle of March the boy had a cold in the head and a cough; he stayed in bed a week, complaining of aching behind both ears. On March 24 he went to the outpatient department of this hospital, where bilateral paracentesis was carried out. After this the temperature was 37.5 to 38 C. (99.5 to 100.4 F.). There was aching of the right ear on March 27; bilateral paracentesis was repeated on the same day. After this there was much suppuration. On March 30 the throat was greatly swollen, and the patient could not hold his head erect. He was admitted to the hospital on the same day and stayed there two days; on discharge he was considered to be almost well, no symptom remaining but slight swelling of the throat. When the child came home from the hospital, the mother noticed that he had bluish red patches on the lower parts of both legs. The boy remained in bed at home; for the first week the temperature was subfebrile; and subsequently it was febrile (38.8 to 39.8 C. [101.8 to 103.6 F.]). There was a slight cold in the head but no cough. After three or four days, the swelling of the throat returned, especially on the right.

When the child was admitted to the hospital his general condition was poor. He was emaciated and apathetic, with a pale grayish skin. The lungs and heart were normal. The abdomen was soft. A large number of fairly soft, tender glands were palpable on both sides of the throat; on the left side they were as large as a plum; on the right, as large as a good-sized hazelnut. On the anterior sur-

faces of the lower parts of the legs were typical efflorescences of erythema nodosum in the process of fading. Suppurative otitis was present on both sides. Lumbar puncture showed normal pressure and yielded normal fluid. The temperature was 40 C. (104 F.). The sedimentation rate was 50. White blood cells numbered 19,770, of which nonsegmentated neutrophils comprised 7 per cent; segmented neutrophils, 73.5 per cent; lymphocytes, 14.5 per cent; monocytes, 4 per cent; eosinophils, 0.5 per cent, and basophils, 0.5 per cent.

The temperature remained between 38 and 39 C. (100.4 and 102.2 F.) except for two days when it was 40 C. (104 F.). The tuberculin reaction to as much as 10 mg. was negative. The patient was transferred on April 24 to the surgical department of Crown Princess Louisa's Hospital for operation on an abscess in the throat. A guinea pig test was made with pus from the incised abscess; no sign of tuberculosis was evident. Roentgen study of the lungs gave negative results.

The boy was retransferred to the Sachs Children's Hospital on May 3, but pneumonia soon developed. This was succeeded by a streptococcic empyema, and the child was taken once more to the Crown Princess Louisa's Hospital (surgical department), where he died on June 1.

CASE 5.—L. E., the brother of the patient just described, was 2 years and 9 months old. He was an inmate of the Sachs Children's Hospital from April 19 to May 28, 1937, because of erythema nodosum, acute pharyngitis, bilateral cervical lymphadenitis and acute bronchitis.

The family history revealed no tuberculosis, and the child was not known to have been exposed to it. The child had previously been well. He had been irritable and fretful since April 12, would not eat and had swelling of the throat. There was no cold in the head or cough. The temperature was not controlled. On a visit to the outpatient department on April 15 the general condition was good. The temperature was 38.1 C. (100.6 F.). There was pronounced acute rhinopharyngitis. The boy was in bed at home with fever for two days, and was then afebrile until the day before admission to the hospital. On April 16 erythema appeared on the lower parts of the legs. The diagnosis at the outpatient department on April 17 was erythema nodosum.

On the child's admission to the hospital his general condition was moderately affected; the skin was pale. The lungs, heart and abdomen appeared normal. On each side of the throat was a moderately tender gland about as large as a mandarin orange, together with a number of glands as large as peas. The tonsils were considerably enlarged and reddened; the pharynx was diffusely reddened. Typical efflorescences of erythema nodosum were present on the lower parts of both legs. White blood cells numbered 17,200, of which nonsegmented neutrophils comprised 11.5 per cent; segmented neutrophils, 35 per cent; lymphocytes, 42.5 per cent; monocytes, 9.5 per cent, and eosinophils, 1.5 per cent. The temperature was 37.4 C. (99.3 F.). The sedimentation rate was 65.

During the whole of the stay at the hospital the patient was afrebile, with the exception of five days when he had acute bronchitis. Roentgen study of the lungs on April 24 gave negative results.

Thus two brothers, in connection with an infection starting from the pharynx, contracted erythema nodosum. In 1 boy the condition became complicated with pneumonia and empyema (streptococcic), and the child died. The brother had less violent symptoms. The tuberculin reaction to 1 mg. was negative.

The case in which death occurred is, of course, of special pathogenic interest.

AUTOPSY

The postmortem examination was carried out by Dr. Wilton.

The diagnoses were chronic indurative and acute purulent tonsillitis; bronchopneumonia of the right lung; empyema with operation; acute bronchiolitis; fibrinopurulent pericarditis, and chronic and acute lymphadenitis.

Gross Examination.—On the left anterior side of the throat was a scar with fibrous transformation of the subcutis. Over an area as large as the palm of a hand, just below the umbilicus, were a few pinpoint hemorrhages in the subcutis. Resection of the ribs had been done on the right. In the operative field there exuded a slight amount of yellowish green pus.

The peritoneum was everywhere smooth and shiny. The liver extended to the costal arch. In the right pleural cavity were about 2 tablespoonfuls (30 cc.) of yellowish green pus. The right lung lay collapsed at the hilus and was completely coated with a thick furring of fibrin. The left pleural cavity was normal. Both the inner surfaces of the pericardial sac, over an area corresponding to the left auricle, were bound together by open-spaced, easily loosened layers of fibrin. In the pericardial sac were about 3 tablespoonfuls (45 cc.) of thin fluid mixed with fibrin.

The heart was of normal size and form. The endocardium was smooth and showed no significant valvular changes. The cardiac musculature was pale gray. The large vessels and the coronary vessels displayed no alterations.

In order to examine the hilar region, the lungs were removed together. On the right was encountered a lymphatic gland about as large as a hazelnut. The sectioned surface was reddened and swollen, and the whole appearance corresponded to that seen with acute lymphadenitis. On section of this gland, nowhere could there be observed any caseous necrosis or other sign of tuberculosis. On dissection of the soft parts in the left hilar region, there could be observed merely a gland as large as a grain of rice, with a firm shiny white sectioned surface, in the center. This gland was kept for microscopic examination, and that on the right, for the guinea pig test. The soft parts of the pharynx were then examined in the same way by dissection along the trachea. Neither below the scar nor in any other place could any lymphatic glands be observed.

The lungs were examined in detail. The upper lobe of the right lung showed a grayish red sectioned surface. The lower lobe was a darker red. The lung parenchyma was atelectatic over large areas. Here and there were elevated areas with a granular cut surface, from which were pressed drops of pus and air-free turbid juice. The left lung was air containing throughout. In the upper lobe, the alveoli were greatly distended by air. From the finer bronchi pus could occasionaly be pressed out. There was no sign of old or recent tuberculosis.

The liver displayed distinct markings, with somewhat distended central veins. The parenchyma was pale brown; it showed no remarkable changes. The spleen weighed 35 Gm. The pulp was somewhat more porous than normal. The ventricle was distended by thin fluid material with a considerable admixture of mucus. The mucous membrane was pale and easily removed from the underlying tissues. In the canal, on the fold of the mucous membrane, were submucous pinpoint hemorrhages. The duodenum displayed a bile-saturated mucous membrane. The biliary ducts and the gallbladder were normal. Neither the small nor the large intestine showed any alterations, with the exception of a few slightly swollen Peyer's patches. At the root of the mesentery there was a lymphatic gland half the size of a pea. The sectioned surface was reddened and slightly swollen. This gland was preserved for the guinea pig test. The kidneys were of normal size.

The sectioned edge was slightly swollen, and in a few places the marking was indistinct. The renal pelves and ureters were normal. The bladder contained a slight amount of turbid disintegrated urine. The mucous membrane showed moderate injection. The adrenals, pancreas and seminal vesicles showed nothing remarkable.

The skull was firmly attached to the dura. In the interstices of the pia was seen a small quantity of clear serous fluid. The meninges were normal. The brain showed no macroscopic alterations.

The mucous membrane of the pharynx was swollen and reddened. The tonsils were as large as hazelnuts; yellow rods issued from the sectioned surface. In the right tonsil was an abscess as large as a grain of rice.

Although the internal organs were examined in detail, it was impossible to find any tuberculous alterations.

Microscopic Examination.—Both tonsils were sectioned. In some places the tonsillar tissue was indurated. There were large numbers of secondary follicles, and infiltration of pus was occasionally noted. The squamous epithelium of the tonsils showed infiltration with white blood cells; here and there was superficial necrosis.

In and around the bronchi of the right lung was infiltrated pus; here and there pneumonia was present in various stages. Both large and small vessels were greatly distended by red blood cells.

The lymphatic gland from the hilar region on the left showed slight induration of the connective tissue in the central parts; otherwise it was normal.

The microscopic investigation, like the macroscopic, failed to show any kind of tuberculous alteration.

A guinea pig test of the hilar and mesenteric glands just mentioned gave negative results.

In view of the careful pathologic, anatomic and histologic investigations together with the guinea pig tests, we believe that tuberculosis may be excluded in this case.

In 4 cases the children complained of more or less troublesome pains in the abdomen, especially on the days before the appearance of the efflorescences. For this reason one of the patients (case 6) was even sent by the doctor to the hospital for suspected peritonitis.

Case 6.—B. Ö., a boy 2 years and 7 months old, was an inmate in the Crown Princess Louisa's Hospital from May 26 to June 11, 1937, because of erythema nodosum.

Two aunts on the father's side, aged respectively 31 and 26 years, had had erythema nodosum, one five years previously and the other in 1936. In both cases roentgen study gave negative results.

At the beginning of May the patient had frequent urination. The urine was dark and turbid and had a strong odor. Some days before the boy's admission to the hospital this symptom disappeared. Simultaneously there was constipation. On May 22 the child complained of pain in the abdomen and had fever (38.3 C. [100.9 F.]). He vomited once. The next day typical efflorescences of erythema nodosum appeared on the lower parts of the legs. The patient complained of pain in the finger joints; the temperature was 38.3 C. The following day the child was sent to the surgical department of the hospital for suspected peritonitis. He remained there from May 24 to May 26. During these days, the temperature was subfebrile. The abdomen was soft but presented tenderness of the lower part on the right side. The urine was normal.

Examination on May 27 showed that the general condition was good. Typical erythema nodosum was present. The lungs, heart and abdomen were normal. The pharynx was pale. On each side of the maxillary angle was a nontender gland half as large as a pea. White blood cells numbered 17,000, of which young myelocytes comprised ⅔ per cent; nonsegmentated neutrophils, 10 per cent; segmentated neutrophils, 48⅓ per cent; lymphocytes, 40⅓ per cent, and monocytes, ⅔ per cent. The urine and feces were normal. The temperature was 37.4 C. (99.3 F.). The sedimentation rate was 60.

During the following week there was fever (38 to 39 C. [100.4 to 102.2 F.]) in connection with an acute pharyngeal infection; afterward the temperature was subfebrile or normal.

The reaction to 3 mg. of tuberculin was negative. A guinea pig test made with the ventricular lavage fluid on May 29 gave a negative result.

On May 27 roentgen study of the lungs showed no abnormality.

It is not easy to judge of the cause of the abdominal pains in these 4 cases when one considers how commonly such abdominal symptoms are associated with acute infections in children, as a rule not least with pharyngeal infections. In cases of erythema nodosum of tuberculous genesis, there occurs now and then another symptom: pain between the shoulders, sometimes even with tenderness over that area. On the other hand, abdominal pains in cases of erythema nodosum of tuberculous origin are unusual; hence the occurrence of such pain in no less than 4 of these nontuberculous children appears to us to deserve mention.

It is remarkable that in a country like Sweden, where for a succession of years it has been demonstrated that the great majority of cases of erythema nodosum have been tuberculous, there should suddenly be discovered in Stockholm, within a brief period, a close succession of cases of erythema nodosum of another type. Of what nature, then, are the cases in which there is a negative reaction to tuberculin?

In case 4, in which a careful pathologic, anatomic and histologic investigation was made, tuberculosis can be excluded. As far as we are aware, there has not previously been reported a case of erythema nodosum in which the tuberculin reaction was negative in which the course, closely corresponding with the erythema nodosum syndrome, has proceeded to death, and in which a careful pathologic and anatomic investigation has been carried out. In our opinion, the case seems to prove that there are instances of erythema nodosum of another origin than tuberculous.

As regards the course of the erythema nodosum syndrome and the result of the clinical investigation as a whole, this case does not differ in any essential respects from the other cases in this group which we have had the opportunity of following or of studying in detail.

Tuberculous erythema nodosum is an allergic symptom complex. In the present cases also, in which there is another cause, there is much which seems to point to the possibility that the erythema nodosum syndrome itself is an allergic phenomenon but is made active by an infection

of another type. According to several of the histories of the cases described here, instances of erythema nodosum had formerly occurred in the family. To a certain degree, this circumstance seems to point to allergy as a cause.

Both in the case in which a pathologic and anatomic investigation was carried out and in several other cases which we have followed, a pharyngeal infection preceded the outbreak of the erythema nodosum. Everything, then, seems to show that a pharyngeal infection can give rise to erythema nodosum. In some of the cases there was no history of a pharyngeal infection; but remembering that a pharyngeal infection may be present in children without being noticed by those in contact with them, we cannot positively exclude the possibility that such an infection preceded the erythema.

The close succession of cases was remarkable in that for a short period in the city where it occurred it altered the previous ratio between tuberculous and nontuberculous erythema nodosum. That such should be the case is interesting and leads to certain consequences. It indicates the necessity of a tuberculin test in every case of erythema nodosum. A Pirquet test or other cutaneous test is not sufficient. If a cutaneous test should give no reaction, the Mantoux test should be performed with 0.1 to 1 mg. Our own experience shows that there are cases of tuberculous erythema nodosum in which the tuberculous allergy is not revealed until a rather large dose of tuberculin is employed. The observations reported here demonstrate that such testing with tuberculin is of more importance than it is at present considered to be. The reason, of course, is that the diagnosis of the condition—tuberculous or nontuberculous—is attended by practical consequences which sometimes are important.

That such a close succession of cases of nontuberculous erythema nodosum could occur in one center of population gives to some extent a new perspective to the problem of erythema nodosum in its entirety.

This circumstance does not nullify the fact that in Scandinavian countries erythema nodosum has, as a rule, hitherto proved to be tuberculous. But our observations seem to imply that one must not exclude the possibility that the relation between tuberculous and nontuberculous erythema nodosum possesses various aspects—aspects which may even vary periodically among different peoples and in different parts of the world.

SUMMARY

It has earlier been shown, particularly by Ernberg's investigations, that erythema nodosum is an allergic syndrome which in the majority of cases is released by a tuberculous infection. At any rate this is true

in children. However, in recent years a number of cases have been described in which the condition seemed to have no connection with tuberculosis.

During the first half of 1937 a rather extensive, close succession of the cases of erythema nodosum in which the tuberculin reaction was negative occurred in Stockholm. During the first six months of that year 34 patients with erythema nodosum were received at the children's hospitals, 20 of whom had negative tuberculin reactions. In these cases the condition occurred during the months of April and May, while in the cases in which the tuberculin reaction was positive the incidence was evenly distributed over the period of January to June.

In comparison we may mention that during the years 1928 to 1936 only 34 of 420 patients treated for erythema nodosum had negative reactions to tuberculin.

The 20 cases of nontuberculous erythema nodosum were subjected to a close analysis, which gave the following results:

Heredity and exposure to tuberculosis played an exceedingly small part. Mantoux tests with from 1 to 20 mg. of tuberculin were carried out with negative results. Roentgen examination of the lungs was made in all these cases, and no changes, or merely unimportant ones, were proved; at any rate they were not of the scope generally associated with tuberculous erythema nodosum. In 1 case the condition was complicated with pneumonia and empyema, and the course ended with death. This case is of special interest, for as far as we know it is the first case of erythema nodosum associated with a negative tuberculin reaction in which postmortem examination was made. At the autopsy, which was carried out with special consideration for the possible existence of tuberculosis, no tuberculous changes could be traced.

To a certain extent these observations throw a new light on the problems of erythema nodosum; they involve important consequences, both from a theoretic and from a practical point of view.

DENTAL CARIES AMONG ESKIMOS OF THE KUSKOKWIM AREA OF ALASKA

II. BIOCHEMICAL CHARACTERISTICS OF STIMULATED SALIVA CORRELATED WITH DENTAL CARIES AND OCCURRENCE OF SALIVARY CALCULUS

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The marked contrast that exists between Eskimos free from dental caries and those among whom the disease is prevalent, as noted in the previous report in this series,[1] makes them particularly desirable as subjects for investigation of the disease, especially in the search for differences to which causative significance may be attached. This report presents the findings in a study of certain chemical characteristics of stimulated saliva of Eskimos with and without dental caries, following the lines indicated in a previous report by one of us.[2] The previous findings showed that the stimulated saliva of persons free from caries differs in several respects, in group averages, from that of persons with active caries. The group without caries yielded higher average values for total calcium, inorganic phosphate, carbon dioxide capacity and percentage of calcium removed after the specimen was shaken with tricalcium phosphate, $Ca_3 (PO_4)_2$, while the group with active caries gave a higher

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Conducted with the aid of grants from the Office of Indian Affairs, United States Department of the Interior, and from the Carnegie Corporation. Detailed acknowledgments were given in the first paper of this series.

This paper is Unit 9, Section IV, of "Dental Studies of the Eskimos of North America," directed by L. M. Waugh, D.D.S., Consultant Dentist, Office of Indian Affairs, and Dental Director (Reserve) of the United States Public Health Service.

1. Rosebury, T., and Waugh, L. M.: Dental Caries Among Eskimos of the Kuskokwim Area of Alaska: I. Clinical and Bacteriologic Findings, Am. J. Dis. Child. **57**:871 (April) 1939.

2. Karshan, M.: J. Dent. Research **15**:383, 1936.

average value for phosphorus removed after similar treatment. The differences between the two groups in the total calcium and the inorganic phosphate content were small, but approached statistical significance, whereas the other differences mentioned were more striking and definitely significant.

METHODS

Samples of saliva for chemical analysis were collected from 49 of the 106 Eskimos used as subjects for the bacteriologic study detailed in the previous report.[1] Under the conditions that obtained in the field, no special precaution could be taken regarding the time of day at which the samples were collected or regarding the relation of the time of collection to meals. A 15 cc. sample stimulated by chewing paraffin was collected immediately after collection of the three minute sample for bacteriologic analysis. After a period of rest ranging up to fifteen minutes, necessarily variable under field conditions, another sample of about 8 cc. was collected. Immediately after collection, 0.05 cc. of a 2 per cent solution of mercury bichloride, added by pipet, was stirred well into each sample, and the tubes were closed with rubber stoppers. The tubes were subsequently sealed with a heavy coating of melted paraffin and shipped to the laboratory in New York for analysis. The period between collection and analysis ranged from nineteen to thirty-seven days. The use of mercury bichloride appeared effectively to inhibit bacterial action; none of the samples, on arrival in New York, showed evidence of decomposition. Preliminary tests had indicated that preservation with mercury bichloride by the method used introduced small and fairly constant changes in the characteristics to be tested. In these preliminary tests, during a period ranging from twenty-eight to thirty-one days, the total calcium content was reduced about 0.3 mg. per hundred cubic centimeters, while the inorganic phosphate content was reduced about 0.6 mg. per hundred cubic centimeters. During fourteen to thirty-one days, the amount of calcium removed after the specimen was shaken with tricalcium phosphate was reduced about 3 per cent, while the corresponding amount of phosphorus was increased about 7 per cent. Carbon dioxide capacity, during twenty-two to thirty-six days, was reduced about 2.3 cc. per hundred cubic centimeters.

The analytic methods used were those described by one of us (M. K.).[2] A single sample of commercial tricalcium phosphate, the same as that used for the previous tests, was employed in all instances.

The subjects studied included 28 who were free from caries, 17 with caries and 4 with doubtful caries, ranging in age from 6 to about 70 years. The basis for selection and classification of these subjects was given in the previous report.[1] It may be pointed out that this basis differed from that previously employed by one of us (M. K.),[2] in which the presence of partially disorganized enamel of early proximal or gingival lesions was taken as an important criterion of carious activity. Since proximal decay of the permanent teeth was comparatively uncommon among the Eskimo subjects of this study and gingival decay was rare, a somewhat less reliable index of activity, softened dentin, was employed. The subjects free from caries were selected on as rigorous a basis as before, however, except that roentgenographic checks were not possible.

RESULTS

In view of the opportunity afforded by the available data to compare both the chemical and the essential bacteriologic findings with the clinical findings, the results are given for individual subjects (table 1). The

TABLE 1.—*Bacteriologic and Chemical Findings in Saliva and Incidence of Dental Caries and Salivary Calculus in Individual Alaskan Eskimos*

Subject	Age, Yr.	Caries, Percentage of Teeth	Calculus	Lactobacilli, No. per Cc. of Saliva	Yeasts, No. per Cc. of Saliva	Total Calcium, Mg. per 100 Cc.	Inorganic Phosphate, Mg. per 100 Cc.	Percentage Removed†		Carbon Dioxide Capacity, Cc. per 100 Cc.
								Calcium	Phosphorus	
L. B.	8	50.0	0	222,600	625	5.5	13.3	76	22	31.2
S. C.	9	66.7	0	20,200	75	5.2	13.2	67	+ 6‡	40.5
I. J.	16	45.8	0	31,050	200	5.8	7.8	67	+21	34.0
M. B.	9	43.3	0	72,400	50	5.1	12.4	72	+12	27.0
F. B.	18	23.3	0	26,300	25	5.6	10.0	71	+16	....
R. I.	12	17.9	0	142,100	175	4.6	11.3	63	15	25.0
K. K.	15	41.7	0	772,630	0	4.6	11.5	56	33	13.6
W. O.	21	31.0	0	479,730	0	5.6	11.0	66	38	13.0
A. L.	20	43.3	0	24,930	0	3.6	13.6	..	45	10.2
E. J.	6	63.8	0	2,500	0	...	....	..	..	40.4
P. T.	7	58.9	0	1,930	0	5.5	12.1	78	+9	31.0
M. T. W.	15	48.2	0	2,800	0	5.7	12.5	47	58	10.8
A. B.	9	20.8	0	775	0	5.1	14.9	52	38	24.5
F. B.	10	58.9	0	0	0	5.3	10.7	43	49	12.6
F. W.	8	17.8	0	0	0	4.8	11.5	66	10	30.8
A. W.	11	16.7	0	0	0	5.4	12.2	64	18	23.0
A. A.	15	48.2	++	0	0	6.3	15.8	76	12	....
E. F.	25	25.0*	0	0	0	5.1	9.6	50	21	21.8
S. W.	22	3.1*	0	0	0	4.8	11.0	45	32	26.0
Kat.	55	0*	+	115,800	0	6.1	11.8	80	+16	43.9
R. W.	41	0*	+	565	50	7.1	13.9	81	19	46.0
N. A.	22	0	++	11,600	0	7.5	13.3	84	+29	56.4
P. K.	9	0	+	2,620	0	5.9	16.7	84	13	45.3
E. W.	6	0	0	750	0	4.8	12.2	54	47	25.8
T. C.	15	0	0	258	0	7.7	11.6	81	9	39.8
Koo.	70	0	±	120	0	7.2	10.0	69	+2	30.0
Fl.	20	0	++	80	0	6.2	10.8	69	12	29.0
Iv.	50	0	0	0	0	5.1	16.2	78	11	22.8
Be.	16	0	±	0	0	5.4	12.8	77	+6	28.7
W. I.	21	0	±	0	0	5.6	14.0	76	12	30.4
Wl.	35	0	±	0	0	6.7	15.0	82	+1	35.4
No name	35	0	±	0	0	4.4	13.2	78	35	27.8
Lo.	40	0	±	0	0	4.8	11.0	72	+62	48.8
Da.	20	0	±	0	0	8.3	14.0	87	35	33.0
Tu.	14	0	+	0	0	4.6	11.9	78	11	35.8
Mo.	18	0	+	0	0	4.9	14.0	61	42	27.0
H. J.	20	0	+	0	0	5.6	14.0	60	42	24.0
Tchu.	30	0	+	0	0	5.7	10.8	70	19	29.8
Phl.	35	0	+	0	0	6.3	13.2	74	+9	46.0
G. W.	36	0	+	0	0	7.8	10.0	73	2	36.8
A. B.	40	0	+	0	0	5.3	12.0	60	16	31.5
Tho.	45	0	+	0	0	10.4	13.8	90	+29	62.0
L. F.	45	0	+	0	0	5.8	13.5	50	12	41.8
S. A.	55	0	+	0	0	6.8	13.7	73	13	32.2
Ma.	18	0	+	0	0	5.8	13.6	75	3	28.0
Jo.	17	0	++	0	0	6.8	9.8	75	+2	28.4
Are.	10	0	++	0	0	5.8	13.7	74	17	44.8
Kang.	14	0	++	0	0	4.2	13.0	71	+18	48.8
Pa.	20	0	++	0	0	5.9	16.7	84	13	45.3

* Doubtful.
† After the specimen was shaken with tricalcium phosphate.
‡ The plus sign indicates that the stated percentage of phosphorus was added during shaking.

data are grouped in accordance with the presence and apparent activity of caries and are listed in an order determined roughly by the bacteriologic findings. Subjects from whom both lactobacilli and yeasts were isolated are listed first, followed by those who yielded lactobacilli

without yeasts and then by those who yielded neither type of organism. The interrelationships of these findings will be discussed later in this paper.

Table 2 presents the average values for the chemical analyses correlated both with dental caries and with the occurrence of salivary calculus.

The average values for the group with caries and for the group without it differed in the same direction as those previously reported for clinic patients. The values for the total calcium and the inorganic phosphate content are similar in magnitude to the averages previously obtained (which for the group with active caries and for that free from dental decay were, respectively, 5.3 and 6.1 mg. for calcium and 12.2 and 13.4 mg. for phosphate [2]). The values for calcium removed after the specimen was shaken with tricalcium phosphate were higher, while those for phosphorus similarly removed were lower, than those previously reported.

TABLE 2.—*Average Values for Chemical Analysis of Stimulated Saliva of Alaskan Eskimos Correlated with Dental Caries and Salivary Calculus*

Condition of Teeth	Number of Subjects	Average Age, Yr.	Total Calcium, Mg. per 100 Cc.	Inorganic Phosphate, Mg. per 100 Cc.	Calcium Removed,* Percentage	Phosphorus Removed,* Percentage	Carbon Dioxide Capacity, Cc. per 100 Cc.
Caries	17	12.3	5.2	12.1	64.3	17.1	24.5
No caries	28	27.7	6.1	12.9	73.7	7.3	36.3
Doubtful caries	4	35.8	5.8	11.6	64.0	14.0	34.4
Calculus 0	21	15.3	5.3	11.9	62.8	19.1	25.2
Calculus ±	7	38.9	6.1	12.9	78.4	1.6	33.5
Calculus +	14	32.9	6.3	13.1	72.1	9.9	37.9
Calculus ++	7	15.7	6.1	13.3	76.2	0.7	42.1

* After the specimen was shaken with tricalcium phosphate.

The averages for carbon dioxide capacity were also higher than the values previously obtained. It may be noted that several of the carbon dioxide values, in particular those obtained among the subjects without caries, are exceptionally high. The maximum individual value recorded previously,[2] 44.7 cc. per hundred cubic centimeters, is exceeded by the results for 8 Eskimos without caries and by 1 with doubtful caries.

In view of the clinical data previously given for these subjects,[1] it is not surprising that the average age of the group with caries was considerably lower than that of the group free from caries. In an effort to determine whether the age factor influences the differences in chemical characteristics, the data for the group without caries were rearranged according to age (table 3). This one group, the largest, was chosen in order that the factor of caries might be eliminated when the effect of age was considered. It appears that only the values for the total calcium content show a trend with age, which may in part account for the difference in the averages between the group without caries as a whole and the group with caries. But even here this effect may be

discounted, since the lowest value given for calcium in table 3—that for the youngest age group, with an average age close to that of the group with caries—is well above the average for the subjects with caries. The other values show no such trend. On the whole, it may be concluded that the differences between the group with caries and that without it given in table 2 are not appreciably determined by the age factor.

Clinical records on the occurrence of salivary calculus being available for these Eskimos, it seemed of interest to regroup the data in relation to that condition. The averages for the four clinical groups, as defined in the previous report [1] are included in table 2. The findings for the total calcium and the inorganic phosphate content are similar to those reported for clinic patients with and without salivary calculus by Tenenbaum and Karshan,[3] although the differences reported here are somewhat smaller. On the whole the findings for the group free from calculus resemble those for the group with caries, and, conversely, the

TABLE 3.—*Relation of Data on Chemical Analysis of Saliva to Age of the Group of Alaskan Eskimos Free from Caries*

Number of Subjects	Age Range, Yr.	Average Age, Yr.	Average Total Calcium, Mg. per 100 Cc.	Average Inorganic Phosphate, Mg. per 100 Cc.	Average Calcium Removed,* Percentage	Average Phosphorus Removed,* Percentage	Average Carbon Dioxide Capacity, Cc. per 100 Cc.
8	6-17	12.6	5.7	12.3	73.9	11.8	36.5
8	18-22	19.9	6.2	13.8	74.5	16.3	34.1
12	30-70	43.0	6.4	12.7	72.4	0.4	37.1

* After the specimen was shaken with tricalcium phosphate.

values for the groups with calculus are similar to those for the group without caries. This is to be expected, in view of the relative distribution of the two clinical conditions among these subjects, as shown in table 1. The 21 subjects free from calculus included 16 of the 17 who had caries, and all but 3 of the 28 subjects with calculus were included in the group without caries. The chemical data thus agree with the indication of the clinical findings, given in the preceding report,[1] that the presence of caries and the occurrence of salivary calculus are inversely related.

Since the subjects with calculus are largely those included in the group free from caries, it appears again that the differences in average age between the groups with differing degrees of calculus do not affect the chemical data. It may be noted that these data indicate trends which are in accordance with increasing amounts of calculus and which are apparently independent of the average age of the four groups.

Statistical analysis of the significance of these data is given for the groups with caries in table 4. The statistical method has been detailed

3. Tenenbaum, B., and Karshan, M.: J. Am. Dent. A. **24**:1255, 1937.

in previous papers.[4] It is based on the assumption of homogeneity of the different groups: that is, on the "null" assumption that the groups to be compared do not differ from one another. Such groups are therefore pooled to derive a common mean (M_o), and the difference (D) between each component mean and the common mean is divided by its standard deviation (σ_D) to determine the probability that the difference observed is not due to chance—i. e., to test the "null" assumption—as indicated in standard tables of probability.[5] On this basis, it appears that the differences between the group with and that without caries in total calcium content and in carbon dioxide capacity are probably significant. The other differences are too small, in relation to the size of the groups tested, to be adjudged significant by this means, although the difference for calcium removed when the specimen was shaken with

TABLE 4.—*Significance of the Average Values for Chemical Analysis of Stimulated Saliva of Alaskan Eskimos in Relation to Dental Caries*

Chemical Constituent	Condition of Teeth	Number of Subjects	Mean	σ_M	M_o	σ_o	D	σ_D	D/σ_D	Odds Against Random Occurrence of Difference
Total calcium	Caries	16	5.2	0.15	5.8	0.18	0.6	0.23	2.61	106 : 1
	No caries	28	6.1	0.24			0.3	0.30	1.00	2 : 1
Inorganic phosphate	Caries	16	12.1	0.47	12.6	0.27	0.5	0.54	0.93	1.7 : 1
	No caries	28	12.9	0.32			0.3	0.42	0.71	1 : 1
Calcium removed	Caries	15	64.3	2.7	70.5	1.6	6.2	3.2	1.94	18 : 1
	No caries	28	73.7	1.8			3.2	2.4	1.33	4 : 1
Phosphorus removed	Caries	16	17.1	6.1	10.8	3.6	6.3	7.1	0.89	1.7 : 1
	No caries	28	7.3	4.4			3.5	5.7	0.61	<1 : 1
Carbon dioxide capacity	Caries	15	24.5	2.7	32.3	1.7	7.8	3.2	2.44	68 : 1
	No caries	28	36.3	1.8			4.0	2.6	1.54	7 : 1

tricalcium phosphate may be considered to approach the level of significance.

A similar analysis of the data in relation to salivary calculus reveals a similar picture, with the differences somewhat less marked, according to statistical standards. When one compares the group free from calculus with a pooled group comprising all those who had calculus, or with the two combined groups of those who had moderate or marked deposits (+ and + +), the differences in total calcium content, in carbon dioxide capacity and in amount of calcium removed after the specimen was shaken with tricalcium phosphate all approach significance, the

4. Karshan,[2] Rosebury, T., and Karshan, M.: Susceptibility to Dental Caries in the Rat: Influence of Calcium, Phosphorus, Vitamin D and Corn Oil, Arch. Path. **20**:697 (Nov.) 1935.

5. Pearl, R.: Medical Biometry and Statistics, Philadelphia, W. B. Saunders Company, 1930, p. 439.

highest individual $D : \sigma_D$ ratios in the three instances being, respectively, 1.79, 2.1 and 2.28. The study of larger groups would be necessary if one were to determine whether these differences are actually significant.

COMMENT

The correspondence between the data reported here for Eskimos and those previously obtained in analyses of the saliva of clinic patients, although incomplete, supports the previous indication that chemical differences, valid for group averages, exist between the saliva of persons with dental caries and that of persons completely free from the disease. The correspondence between the two sets of findings is noteworthy in view of the different basis for classification of cases used in this investigation, the criteria being necessarily somewhat less exacting than those previously used with respect to the activity of caries. The findings as a whole augment the evidence, detailed in the preceding report in this series,[1] that caries among the Eskimos is essentially the same disease as caries among other peoples. It is interesting that the differences in the salivary characteristics studied between the group of Eskimos with caries and the group without the disease are in all instances similar in direction to those reported previously. That several of the actual average values differ considerably in magnitude from the averages previously obtained may reflect conditions peculiar to Eskimos or to certain Eskimos. We are not able to explain these findings on other grounds.

The statistical analysis of the salivary data in relation to caries indicates that two of the five differences observed between the group with caries and the group free from the disease are probably significant, while a third borders on significance. The former are the total calcium content and the carbon dioxide capacity, and the latter is the percentage of calcium removed from saliva after the specimen was shaken with tricalcium phosphate. Such an analysis, with each salivary characteristic considered separately, may not indicate the whole significance of the findings. Thus, further evaluation of the data given in table 2 reveals that 57, or 79 per cent, of the individual chemical values for the group with caries lie on the caries side of the pooled means (M_o in table 4); all 16 of the subjects in this group yielded values of this order for two or more of the five characteristics; 11, or 69 per cent, showed the correspondence for three or more characteristics, and 6, or 38 per cent, showed what may be called typical values for all five. For the group without caries the correspondence was less striking. Here, 75, or 55 per cent of the values, were on the caries-free side of the means; 16 of the 28 subjects, or 57 per cent, gave typical values for three or more of the characteristics, whereas only 4, or 14 per cent, showed

the correspondence for all five characteristics and 3 of the subjects gave values consistently on the caries side of the means.

The findings reported here augment the data of several investigators [6] who observed that the saliva of persons with active dental caries differs in certain chemical characteristics, in group averages, from that of persons free from dental decay. The meaning of the recorded differences with respect to the mechanism of caries is not as yet entirely clear. Their direction is such as to indicate that they are related in some way to the solubility or the destructibility of dental enamel. Thus, higher levels of salivary calcium and inorganic phosphate, as found in groups without caries, would tend to reduce the solubility of dental enamel in a medium to which the saliva has access. A higher carbon dioxide capacity, likewise, indicating a higher bicarbonate content, would increase the acid-neutralizing potency of the saliva and thus would tend to limit the development of p_H levels at which the enamel is attacked. Presumably, the partition values for calcium and phosphorus reflect the forms in which these elements occur in saliva, but their meaning in relation to dental caries is uncertain.

The bacteriologic data were included in table 1 in order that they might be compared with the chemical and the clinical findings. That the occurrence and concentration of lactobacilli are clearly correlated with the presence of dental caries was indicated in the preceding paper in this series [1] and can be seen in the results for the partial groups presented here. Since the chemical data also appear to be correlated with caries, it is interesting to compare directly the chemical with the bacteriologic data. There appears, however, to be little individual relationship between them, so far as these data indicate. Thus, the last 4 subjects in the group with caries shown in table 1, who failed to yield lactobacilli, resembled the group as a whole in the general aspect of their chemical data. Of the 6 subjects whose chemical values were all on the caries side of the pooled means—i. e., of the 6 chemically "best" subjects with caries—although 5 yielded lactobacilli, for 2 of these there were rather low counts. In the group without caries, moreover, the chemical values for the 6 subjects whose cultures yielded lactobacilli were again not particularly distinctive: For 1 of them all five chemical values were on the "caries-free" side of the means, but for another all five were on the other side. One may thus infer that the two groups of data, the chemical and the bacteriologic, reflect two separate mechanisms, which are dissimilar, although both may be related to the activity of dental caries.

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6. Karshan.[2] Karshan, M.; Krasnow, F., and Krejci, L. E.: J. Dent. Research **11**:573, 1931. Krasnow, F.: ibid. **12**:530, 1932. Hubbell, R. B., and Bunting, R. W.: J. Nutrition **5**:599, 1932. Hubbell, R. B.: Am. J. Physiol. **105**:436, 1933.

SUMMARY

Analysis of the stimulated saliva of 49 Eskimos yielded higher average values for the group free from dental caries, as compared with the group having active caries, for the total calcium content, the inorganic phosphate content, the carbon dioxide capacity and the percentage of calcium removed after the specimen was shaken with tricalcium phosphate, as well as a lower average value for the group without caries for phosphorus removed after the same procedure. The differences in average values between the two clinical groups are similar in direction to those previously reported for clinic patients. Statistically the differences in total calcium content and in carbon dioxide capacity appear significant, while the difference in calcium removed after the specimen was shaken with tricalcium phosphate approaches a significant level. These findings thus confirm the previously reported indication that certain salivary characteristics, presumably related to the power of saliva to prevent the solution of dental enamel by acids, are correlated in group averages with the occurrence of dental caries. They also augment the clinical and bacteriologic evidence, presented in the preceding paper in this series, that dental caries among Eskimos is similar to dental caries elsewhere.

In addition, the same data correlated with the presence of salivary calculus show average differences such that the group free from calculus resembles the group with active caries in these chemical characteristics, while the groups with calculus in varying degree resemble the group without caries. Thus weight is added to the evidence for the inverse relationship between caries and salivary calculus previously noted on clinical grounds.

The data on the occurrence of lactobacilli and yeasts in the saliva of these 49 Eskimo subjects are presented individually with the chemical findings. Although both the bacteriologic and the chemical data separately appear to be correlated with the occurrence of dental caries, the two groups of data show little correspondence with each other for the individual subjects.

ERYTHROCYTES IN URINARY SEDIMENT IN HEALTH AND IN DISEASE (SCARLET FEVER)

STUDIES BY THE ORTHOTOLIDINE TEST

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The cause of chronic glomerular nephritis is by no means clear, nor is there much agreement among investigators as to whether an acute attack followed by a latent period is the forerunner of the chronic stage. It is not the purpose of this article, nor will any attempt be made, to discuss exhaustively the literature on these problems. We present, however, a few expressions of opinion from recent textbooks and articles relating to the subject. Aldrich [1] stated:

> Several facts brought out by our study of nephritis have cast doubt upon this hypothesis: First, one is often unable to elicit from the patients or their families any history of acute febrile infection at the onset; second, our careful follow-up observation of large numbers of children who have suffered from acute postinfectious hemorrhagic nephritis has failed to reveal significant relationship between the two conditions; third, in the few patients seen from the beginning of their chronic nephritis, the onset observed was distinctly insidious; fourth, treatment in our clinic of all demonstrable foci of infection has never had perceptible favorable influence on the course of chronic nephritis or resulted in a single cure.

Boyle, Aldrich and their co-workers [2] studied by means of Addis counts 25 children clinically recovered from acute hemorrhagic nephritis, the studies being made up to eight years after recovery. They concluded that children who have clinically recovered from acute postinfectious hemorrhagic nephritis do not have subacute or latent nephritis.

Fishberg [3] concluded:

> The etiology of acute glomerulo-nephritis, from which the chronic form evolves, has been discussed. Chronic glomerulo-nephritis seems more apt to develop

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From the Sarah Morris Hospital for Children of the Michael Reese Hospital and the Cook County Children's and the Cook County Contagious Disease Hospital.

1. Aldrich, C. A.: Chronic Nonspecific Nepritis, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., vol. 3, chap. 28, p. 11.

2. Boyle, H. H.; Aldrich, C. A.; Frank, A., and Borowsky, S.: The Addis Count in Children Following Clinical Recovery from Postinfectious Nephritis, J. A. M. A. **108**:1496 (May 1) 1937.

3. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1934, pp. 427-429.

after certain varieties of the acute disease than following others. Thus, post-scarlatinal glomerulo-nephritis becomes chronic in only an exceedingly small proportion of cases. Chronic glomerulo-nephritis is apparently more likely to evolve when the acute attack follows sore throat or exposure to cold. . . . I have the impression that acute glomerulo-nephritis in older individuals is decidedly more apt to become chronic than in the young. . . . While there are many cases of chronic glomerulo-nephritis in which the evolution from the acute stage occurs under our eyes or can be traced with fair certainty from the history, there is also a large contingent in which no history of the acute attack can be obtained. In such cases, it is probable that the acute attack was so mild that it never came to the attention of the patient. The initial renal injury may have followed a sore throat which was considered merely an insignificant "cold" for which a physician was not consulted. Possibly, also, some of the cases date from scarlet fever in childhood.

Murphy [4] remarked:

The milder forms [of acute nephritis] may pass unrecognized and untreated, and neither the patient nor the doctor may know that there is any disease of the kidney. These are the cases which frequently progress insidiously into the chronic form. It is generally believed at present that the chronic form of glomerular nephritis develops as a result of an acute attack which remains unhealed. A study of patients with chronic nephritis shows that in most cases a history of an acute attack is lacking. . . . Escaping recognition, the first evidence of renal damage appears months or years later with the development of the symptoms and signs of chronic glomerular nephritis. . . . The severity of the initial attack is not a deciding factor with regard to the course and outcome of the disease . . . a mild, almost unrecognizable acute attack may gradually pass over into the chronic phase, while in some of the most severe attacks healing occurs promptly . . . a clinical cure does not mean that the renal lesion has healed. . . . The unhealed lesion may smoulder for months or years without giving any pronounced evidence of its presence.

Snoke,[5] working with Addis, was one of the most recent contestants of the view of Aldrich [6] and Guild [7] that the prognosis of acute nephritis in children, at least, is almost uniformly good for complete recovery and that chronic nephritis is an entity etiologically unconnected with acute glomerular nephritis. Snoke pointed out that Addis was the first to offer proof that acute nephritis and chronic nephritis are, respectively, the beginning and the last stage of one continuing process. The connecting link was supplied by Addis,[8] who discovered and applied a

4. Murphy, F. D.: Acute Diffuse Glomerular Nephritis, M. Clin. North America **18**:1331 (March) 1935.

5. Snoke, A. W.: Stages, Prognosis and Duration of Glomerular Nephritis in Childhood, Am. J. Dis. Child. **53**:673 (March) 1937.

6. Aldrich, C. A.: Clinical Types of Nephritis in Childhood, J. A. M. A. **94**:1637 (May 24) 1930.

7. Guild, H.: The Prognosis of Acute Glomerular Nepritis in Childhood, Bull. Johns Hopkins Hosp. **48**:193 (April) 1931.

8. Addis, T.: A Clinical Classification of Bright's Disease, J. A. M. A. **85**: 163 (July 18) 1925.

suitable quantitative test for pathologic elements in the urine. He established the existence of a latent stage in nephritis during which casts, red blood cells, epithelial cells and protein are excreted in abnormally large amounts for periods ranging from a month to twenty years or more, thus demonstrating continuing activity of the renal lesion. During this period the patient remains in apparently good general health, and the ordinary tests for renal function indicate that the kidneys are normal. Addis observed that in some cases the latent stage is followed by actual and apparently complete healing. In others he was able to trace a continuously active process through the acute, latent and chronic stages and the final uremic episodes.

The latent stage of nephritis is that in which there is absence of symptoms together with the continuing excretion of abnormally large numbers of red blood cells, casts and protein, which usually cannot be determined without the use of the Addis count, by the concentration method. Snoke,[8a] after performing the Addis count on many children, concluded that acute glomerular nephritis in children commonly, if not invariably, enters a latent stage after the initial period. It may heal during the latent stage. The initial stage, no matter how intense, gives no indication of the ultimate prognosis.

Lyttle,[9] using the Addis sediment count, found for normal children that the average number of red blood cells in the twelve hour concentrated night urine was 15,181, with a maximum of 129,000, as compared with 500,000 cells, the maximum normal figure of Addis for adults. Lyttle,[10] after performing the Addis sediment count on 14 children who were recovering from scarlet fever, found that all tests showed moderate transient increases in the excretion of protein and formed elements during the period from eight to forty-five days after the onset of scarlet fever. In none was there the slightest clinical evidence of nephritis. He stated that experience has indicated that in many cases the information yielded justifies the added expenditure of time from the standpoint of both therapy and prognosis. The Addis count is only approximately accurate, and even Addis pointed out that it is unnecessary to make the method quantitative in the strict sense of the word. The figures are roughly approximate and are highly suitable for clinical purposes.

Consequently it is obvious that the Addis sediment count or an equivalent test is valuable when the purpose is: (1) to detect latent

8a. Snoke, A. W.: Prognosis of Chronic Glomerular Nephritis in Children, J. Pediat. **14**:111 (Jan.) 1939.

9. Lyttle, J. D.: The Addis Sediment Count in Normal Children, J. Clin. Investigation **12**:87 (Jan.) 1933.

10. Lyttle, J. D.: The Addis Sediment Count in Scarlet Fever, J. Clin. Investigation **12**:95 (Jan.) 1933.

nephritis; (2) to follow the transition from acute to chronic nephritis through the latent stage; (3) to determine the complete recovery or healing of the kidneys; (4) to detect the effects of therapeutic procedures or pharmaceutics on the kidneys in health and disease; (5) to determine the incidence and duration of mild, clinically unrecognizable (subclinical) nephritis during the course of or following acute infections (this might explain the development of chronic nephritis without a history of an acute stage), or (6) to differentiate between true nephrosis and the nephrotic component of chronic glomerular nephritis. The picture of nephrosis, except for the presence of hematuria, is often closely simulated for a time by the degenerative phase of glomerular nephritis. The two conditions can be distinguished in many instances only by the Addis concentration count or its equivalent carried out over a considerable period (repeated examinations). Differentiation of the two is of great importance, since nephrosis is a reversible disorder, subject to spontaneous recovery, whereas the other disease has an extremely grave prognosis. The presence or absence of hematuria is absolutely vital in making the prognosis.

However, there is a distinct disadvantage in the Addis sediment count. It is so time consuming that it is impracticable for office practice, or even ordinary hospital and clinical work, unless a special technician can devote many hours to it. If there is ever to be a successful solution of this important problem of the relation of acute, subclinical, latent and chronic nephritis, it will depend on numerous observations on the urine of many patients over long periods both in clinical and in office practice, much of which will of necessity have to be done by busy practitioners. No one person will probably ever have enough cases in any individual clinic. In short, the labor entailed in counting red cells in urinary sediments restricts the usefulness of the method in clinical work. Consequently, a simpler, less time-consuming test than the Addis count, one about equally satisfactory, is welcome.

DESCRIPTION OF ORTHOTOLIDINE TEST

In our estimation, Stone and Burke[11] have elaborated such a test. Orthotolidine, an inexpensive chemical obtained from the research laboratory of the Eastman Kodak Company, Rochester, N. Y., will detect minute quantities of blood and hemoglobin in urinary sediments.

The urine is collected as for an Addis count. When this test is done with children, fluid is withheld during the afternoon and night except for 200 cc. given at an early evening meal; a sample of urine collected between 7 p. m. and 7 a. m. will usually contain about 400 cc. of urine

11. Stone, W. J., and Burke, G. T.: An Improved Test for Occult Blood, Especially in Urine, J. A. M. A. **102**:1549 (May 12) 1934.

with a hydrogen ion concentration between 5 and 6 and a specific gravity well above 1.020. The urine is sufficiently acid and concentrated that most of the red cells will not disintegrate. The concentrated night urine is thoroughly shaken and mixed.

According to Stone and Burke, the test is performed as follows:

1. Orthotolidine 1 per cent in chemically pure methyl alcohol. (It dissolves with slight difficulty and keeps at least ten months.)

2. Glacial acetic acid one part and commercial hydrogen peroxide two parts. (This keeps for three or four months, probably longer.)

3. Fifteen cc. of urine is centrifugated at about 1,500 revolutions per minute for five minutes. The supernatant fluid is poured off. A portion of the sediment is prepared for microscopic examination in the usual way. To the remaining sediment two drops of the orthotolidine solution is added plus two or three drops of the acid-peroxide solution. In the presence of blood cells aggregating 100 per cubic millimeter of sediment (approximately 1,350 per cubic centimeter of urine) a greenish blue color develops, lasting about one minute. In the presence of from 300 to 500 red cells per cubic millimeter of sediment (approximately 4,000 to 6,500 cells per cubic centimeter of urine) a deeper blue color develops lasting about one minute. In the presence of larger numbers of red cells, aggregating 1,000 per cubic millimeter of sediment (approximately 13,000 per cubic centimeter of urine) as in hemorrhagic Bright's disease (glomerulonephritis) a deep blue color develops lasting two minutes or longer.

Undiluted blood serum, 10 per cent sodium hydroxide, strong trisodium phosphate solutions and probably other strong alkalis will give positive reactions. Pus cells or any of the common organic or inorganic constituents found in the urine do not give positive reactions. [Iodides and bromides eliminated in the urine may at times cause a confusing blue-black color. The erythrocytes in] specimens of urine containing as high as 5,000 red cells per cubic centimeter will in most instances be undetected by the usual microscopic examinations, since such numbers may represent only one or two cells per high power field.

The color change is so sensitive that once a strongly positive reaction has been obtained in a glass centrifuge or test tube the container must be thoroughly washed and scrubbed with soap and water a number of times before the drops of wash water collecting at the bottom and sides will not give a bluish color when the reagents are again added. All the glass apparatus to be used, especially after a positive reaction has been obtained, must first just be tested with the reagents before the apparatus is used again in order that one may be certain that no bluish color will develop.

EXPERIMENTAL WORK

We made many dilutions of red blood cells by adding definite numbers of cells to definite amounts of a physiologic solution of sodium chloride and then centrifuging 10 to 15 cc. for five minutes at 1,500 to 1,800 revolutions per minute. For the purposes of this paper, only the extremely dilute solutions will be considered. When 500,000 erythrocytes were added to 500 cc. of solution of sodium chloride, the centrifuged sediment gave a light blue color, which persisted for about

ten seconds, when the orthotolidine reagents were added. The benzidine test gave a negative reaction and no red cells could be seen under the microscope. When 250,000 erythrocytes were added to 500 cc. of a physiologic solution of sodium chloride, the addition of the orthotolidine reagents to the centrifuged sediment gave a very light blue reaction, which faded within five seconds; the benzidine test gave a negative reaction, and no cells were seen under the microscope. When 125,000 red cells were added to 500 cc. of solution of sodium chloride, the orthotolidine test repeatedly gave negative results with the centrifuged sediment, as did, of course, the benzidine test. When 5,000,000 cells were added, both the orthotolidine and benzidine test gave a strongly positive reaction, but only 1 or 2 red blood cells could be detected microscopically in the centrifuged sediment.

TABLE 1.—*Results of Tests for Red Blood Cells in a Physiologic Solution of Sodium Chloride*

No. of Erythrocytes in 500 Cc.	Results of Orthotolidine Test	Results of Benzidine Test	No. of Red Cells Seen on Microscopic Examination
5,000,000	++++	++++	1 to 2 per high power field
500,000	+ (faded in 10 to 15 sec.)	0	None
250,000	Trace (faded in 5 sec.)	0	None
125,000	0	0	0

STUDIES ON URINARY SEDIMENT OF CHILDREN CONVALESCING FROM SCARLET FEVER

The orthotolidine test was performed by one of us on a group of patients (mostly children) convalescing from scarlet fever at the Cook County Contagious Disease Hospital (permission of Dr. A. L. Hoyne). The results are tabulated in table 2.

Summary of Results.—The studies on the urinary sediment of patients who were convalescing normally from scarlet fever, none of whom had the usual clinical or laboratory evidence of acute nephritis, may be summarized as follows:

1. The concentrated acid night urine of 44 per cent contained at least more than 125,000 erythrocytes per 500 cc., and the urine of most of the patients with positive reactions contained more than 250,000 red blood cells per 500 cc. at some time during the second, third or fourth week. As we have found that the orthotolidine test gives negative reactions with the vast majority of tested specimens of urinary sediment of children who are enjoying normal health, the positive reactions indicated pathologically large amounts of erythrocytes in the

urinary sediment of a considerable number of children who were convalescing normally from scarlet fever.

2. The highest total incidence (34.6 per cent) of the pathologic increase of red cells in the urinary sediment occurred during the third week, coinciding in time with the highest incidence of clinical nephritis during scarlet fever, although the highest number of positive reactions (28.7 per cent) appeared for the first time during the second week as compared with the number of positive reactions (16.7 per cent) which appeared for the first time during the third week.

TABLE 2.—*Results of Orthotolidine Test on Urine of Patients Convalescing from Scarlet Fever* *

	Second Week	Third Week	Fourth Week
Total number of patients.....	202	202	202
Total number of patients with positive reactions	58 (28.7%)	74 (34.6%)	39 (14.3%)
Number of patients whose reactions became positive after being negative in second week....		35 (16.7%)	6 (2.9%)
Course of patients whose reactions were positive in second week		Reactions of 27 became negative in third week; those of 31 remained positive	Reactions of 38 were negative in fourth week; those of 20 remained positive (34% of those whose reactions were positive in second week)
Course of patients whose reactions were negative in second week (144)		Reactions of 35 (24.3%) became positive for first time in third week	Reactions of 6 (4.2%) became positive for first time in fourth week
Course of patients whose reactions first became positive in third week		.....	Reactions of 22 became negative in fourth week; those of 13 remained positive in fourth week
Number of patients whose reactions first became positive in fourth week after being negative in second and third weeks.....			6
		Occasional Red Blood Cells	Casts
Number of patients with positive reactions whose urine showed microscopic red cells or casts in centrifuged sediment (high power field).....		8 of 202 (3.9%)	None of 202

* The test was carried out according to the method described in the text. In no case could the condition be classified as clinical nephritis, either clinically or by the routine examinations of urine done at the laboratory of the Cook County Contagious Disease Hospital. Cases in which clinical nephritis occurred during the period of investigation were not included. All the patients studied were afebrile and were enjoying normal convalescence.

3. The small number of patients (2.9 per cent) whose reactions became positive for the first time during the fourth week probably indicates that the danger that acute nephritis will develop more than three weeks after the onset of scarlet fever is minimal.

4. About one half of the patients whose reactions became positive during the second week had negative reactions during the third week, and approximately one third of those whose reactions became positive during the second week continued to have positive reactions in the fourth week. About half of those whose reactions became positive for the first time in the third week continued to have positive reactions in the fourth week.

5. Unfortunately, facilities were not available for the follow-up study of the patients (14.3 per cent) who still had pathologic urinary sediment during the fourth week, as the children were discharged from the hospital in twenty-eight days. The number of children who will maintain abnormal urinary sediment for a prolonged period and will later have chronic nephritis deserves careful follow-up study by those who have the proper setup for such work.

6. The strikingly small number of specimens of pathologic urinary sediment which were detected by the ordinary high power examination of the centrifuged sediment (Addis counts were not done, however) again demonstrates the value of a rapid clinical test to supplement the usual microscopic examination.

COMMENT

The Addis sediment count on the urine is acknowledged to be only an approximately quantitative test, but one sufficiently accurate for all practical investigative purposes. Its main disadvantage is that it consumes much time, the labor entailed restricting its usefulness in clinical work. The orthotolidine test in our hands has proved to be as reliable as the Addis count with regard to the erythrocytes, and it requires only a few minutes. We believe, therefore, that the orthotolidine test on urinary sediment could and should be much more extensively used in office, hospital and clinical practice in order that in thousands of cases, rather than in the few thus far studied, the following problems may be investigated: (1) the incidence and duration of subclinical nephritis following minor infections, such as colds and sore throat, as well as after more severe streptococcic conditions such as tonsillitis and scarlet fever; (2) the incidence and duration of latent nephritis following acute clinical glomerulonephritis and the complete healing of the kidneys in these cases; (3) the missing link (latent nephritis) between the acute and the chronic type of glomerulonephritis (with private patients who have "recovered" from acute nephritis reporting once every six months to a year for many years and clinical patients returning to a nephritis clinic); (4) the more accurate differentiation between chronic glomerulonephritis in the nephrotic stage and true nephrosis, and (5) the determination of the effects of various kinds of therapy on the course of glomerulonephritis.

We should welcome repetition and elaboration of our work on a large scale by other investigators, to confirm or criticize the comparative values of the orthotolidine test and the Addis count in determining the number of red blood cells in the urinary sediment, because of the tremendous value of these tests in solving many of the problems of glomerulonephritis and because of the ease with which the orthotolidine test can be performed.

SUMMARY AND CONCLUSIONS

The relation of acute and chronic glomerulonephritis is discussed. There is still much difference of opinion as to whether the former is always a forerunner of the latter, especially in children.

The Addis urinary sediment count is discussed. It is quantitatively approximately accurate, but is time consuming.

The orthotolidine test, as elaborated by Stone and Burke, is described. This is a rapidly performed, accurate test for determining the limits between normal and pathologic urinary sediments with regard to erythrocytes.

It has been determined that the reaction to the orthotolidine test becomes faintly positive in the centrifuged sediment when there are 250,000 erythrocytes per 500 cc. of fluid.

It has been determined that the concentrated urinary sediment of the great majority of healthy children tested gives a negative orthotolidine reaction.

Results of the orthotolidine test on the urinary sediment of 202 children who were convalescing normally from scarlet fever are tabulated and discussed. Ninety-nine, or 44 per cent, had abnormal urinary sediment at some time during the second, third or fourth week.

A plea is made for much wider use of this test as an aid in solving many problems encountered in cases of glomerulonephritis.

MARBLE BONES

II. CHEMICAL ANALYSIS OF BONE

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The term "marble bones" refers to certain gross physical characteristics of the bone in osteopetrosis rather than to its actual chemical composition or to the crystal structure of its inorganic matter. Although several postmortem examinations have been made in cases of this condition, few complete reports on the chemical composition of the bones are available. McCune and Bradley [1] collected 5 cases in which analyses of bone had been made. In 1 of these only the calcium determination was reported. In another case the calcium, phosphorus, magnesium, carbon dioxide and water contents were determined. The results justify suspicion as to their accuracy. The only report of a case resembling our own was made by Clifton and Frank from analyses by Smith Freeman. In their monograph on marble bones [2] the following statement appears:

> The chemical composition of the bone ash in osteopetrosis as determined by our own observations and those of others is within normal limits; however, we found the per cent ash high for the more distinctively pathologic bone.

PURPOSE OF INVESTIGATION

Postmortem examination of the patient to be described offered an opportunity to perform complete quantitative chemical analyses of the various bones, particularly of those showing the typical lesion of osteopetrosis. For comparison, it was necessary to perform similar analyses on the bones of infants who were of approximately the same age but were free from this disease. Our objective was threefold:

From the Pediatric Research Laboratory of the Jewish Hospital.

1. McCune, D. J., and Bradley, C.: Osteopetrosis (Marble Bones) in an Infant: Review of the Literature and Report of a Case, Am. J. Dis. Child. **48**: 949 (Nov.) 1934.

2. Clifton, W. M., and Frank, A.: Osteopetrosis, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1936, vol. 4, chap. 23, sect. 2, p. 26.

(1) to determine the chemical composition of the inorganic material (a factual aim); (2) to provide, if possible, an explanation for the peculiar properties of this bony material, such as its roentgen and histologic appearance and its brittleness, and (3) to elucidate the mechanism of the disease.

PROCEDURE AND CHEMICAL METHODS

The bones were removed from the body a few hours after death. The adherent tissues and cartilage were carefully scraped off, and the bones were dried to a constant weight at 105 C. The dried bones were broken up and ground with a mortar and pestle to a powder of about 80 mesh. Samples of approximately 0.5 Gm. of the dried powdered bone were weighed into previously weighed extraction thimbles and were extracted in a Soxhlet extraction apparatus with acid-free alcohol and acid-free ether (four hours each). The loss in weight represents the amount of fat extracted. (The extraction thimbles take up water while they are being weighed; consequently, we always placed the thimbles in large weighing bottles which had been properly tared.)

The rest of the analysis was done on the dried, powdered, defatted bone. Samples of approximately 0.5 Gm. each were weighed out directly into beakers and were dissolved in 5 normal hydrochloric acid by being heated on a steam bath for several hours. Five cubic centimeters of a 10 per cent solution of trichloroacetic acid was added to precipitate the proteins. The solution of bone was then filtered and transferred quantitatively into a 100 cc. volumetric flask. One cubic centimeter was carefully withdrawn for estimation of the total base by the electrometric method.[3] The remaining 99 cc. was transferred to a beaker, and the calcium, magnesium and phosphate contents were determined. The analytic procedure followed was that of Washburn and Shear.[4] Known mixtures had been analyzed by this method, which was shown to have the following degrees of precision: for calcium, $\pm$ 0.5 per cent; for phosphorus, $\pm$ 0.5 per cent and for magnesium, 2 per cent (for such small amounts as are present in bone). The analysis of each bone was done in duplicate.

Determinations of carbonate were done separately in 20 mg. samples of bone powder by the manometric method of Shear and Kramer[5] with a precision of $\pm$ 3 per cent. A separate sample of the dried, powdered, defatted bone was ashed in a muffle furnace at 500 C. for forty-eight hours in order that the percentage of ash might be determined.

We analyzed the bones of a child who died of the infantile form of osteopetrosis (marble bones). For comparison, results obtained with the bones of a number of subjects, including a fetus, a 5½ hour old infant, a 6 day old infant, a 10 year old child and a 24 year old adult, will be presented. Because of possible differences in the composition of different bones of the same subject, the results with corresponding bones were tabulated. Because of marked fluctuations in the water content of different bones, all analyses for calcium, magnesium, phosphate and carbonate were performed on dried, fat-free bone and are so expressed. Blocks of all bones analyzed were decalcified and examined histologically.

3. Keys, A.: J. Biol. Chem. **114**:449, 1936.
4. Washburn, M. L., and Shear, M. J.: J. Biol. Chem. **99**:21, 1932.
5. Shear, M. J., and Kramer, B.: J. Biol. Chem. **79**:105, 1928.

Calculations were made as follows:

Residual calcium = total calcium — calcium combined with CO_2 as $CaCO_3$

Residual phosphorus = total phosphorus — phosphorus combined with magnesium as $Mg_3(PO_4)_2$

If it is assumed that the magnesium is present as $MgCO_3$, residual calcium = total calcium — (calcium combined with CO_2 as $CaCO_3$ after the CO_2 necessary for the formation of $MgCO_3$ has been subtracted)

Residual phosphorus = total phosphorus

In the formula $CaCO_3.n[Ca_3(PO_4)_2]$,

$$n = \frac{\text{mols of } Ca_3(PO_4)_2}{\text{mols of } CaCO_3} = \frac{\frac{1}{3} \text{ residual calcium}}{\text{calcium combined with } CO_2}$$

Calculated ash = Ca^{++} + Mg^{++} + (P as Po_4—) + (CO_2 as CO_3—)

Water content = loss of weight of cleaned bone after it has been dried to constant weight at 105 C.

Fat content = all material extractable by ether and alcohol

Ash = residue after dried bones have been in a muffle furnace at 500 C. for forty-eight hours

RESULTS

Ash.—There was excellent agreement between the ash content as determined directly and as calculated on the assumption that the carbonate exists as calcium and magnesium carbonate and that all the inorganic phosphorus is present as tertiary calcium phosphate. Because of this, we occasionally used the calculated ash content when we had failed to determine the ash content directly. In 4 instances the ash content of the ribs varied only between 58 and 61.5 per cent, although the ages of the subjects varied from 5½ hours to 29 years. The ash content of the tibia of our patient, R. H., was 65.6 per cent; i. e., it was higher than that of the normal newly born infant. The pathologic petrous bone again showed a distinctly higher ash content than the petrous bone of the newly born infant. It is important to note that the ash content of the "marble bone" was in no instance higher than that of the corresponding bones in the fetus [6] but was higher than the ash content of the corresponding bones of the newly born infant.

The calcium contents of the ribs of all our subjects varied only between 21.96 and 22.74 Gm. per hundred grams of bone. Toverud and Toverud [7] reported an average calcium content of 21.65 Gm. per hundred grams of fat-free dried ribs of infants born at full term of mothers who received a fairly good diet during pregnancy. The calcium contents of the bones of these newborn infants were only slightly influenced by the nature and adequacy of the mothers' diets during pregnancy. Prematurity exerted a greater influence than did the maternal diet. This influence was nevertheless slight. A similar pro-

6. This observation is not in agreement with the previous reports on the ash content of bones of prematurely born infants.

7. Toverud, K., and Toverud, G.: Acta pædiat. **16**:459, 1933.

tective influence of the maternal organism in favor of the skeleton of the offspring has been reported by Booher and Hansmann.[8] These observers reported an average calcium content of 16.74 Gm. per hundred grams of dry fat-free tibia with a coefficient of variation of 1.4 in one group and a value of 16.48 Gm. with a coefficient of variation of 2.5 in another group. The difference between their values and our own may have been due to the preliminary treatment of the basic material. The inorganic phosphorus content of the dried fat-free ribs

TABLE 1.—*Inorganic Composition of Normal Rib Bone: Effect of Age* *

	Fetus‡	Newborn Infant	Newborn Infant	Child	Adult
Age of subject	16-18 wk.	5½ hr.	6 days	10 yr.	29 yr.
	Gm. in 100 Gm. of Bone				
Water	31.10	32.30	(17.10)§	32.80	34.97
Fat	4.11	3.57	.....	0.08	4.36
Analyses done on dry, defatted bone					
Ash	64.50 (Calculated)	57.75	60.12	61.50	58.80
$\frac{\text{Residual Ca}}{\text{P}}$ †	1.94	1.89	1.96	1.94	1.93
(Assuming all magnesium bound to carbonate)					
$n = \frac{\text{⅓ residual calcium}}{\text{Ca combined with } CO_2}$	3.39	2.98	2.56	2.45	2.08

* This table shows how the value of n decreases with age. It also shows the striking constancy of the calcium-phosphorus ratio. Precision = 1.94 ± 0.027.[9]

† $\frac{\text{Ca}}{\text{P}}$ can be calculated in two ways:

$\frac{\text{Residual Ca}}{\text{Residual P}} = \frac{\text{(Total Ca − carbonate Ca)}}{\text{(Total P − P as } Mg_3[PO_4]_2)}$

or

$\frac{\text{Residual Ca (with respect to } CO_2)}{\text{Total P}}$ = Total Ca − Ca bound to the carbonate remaining after all Mg combines with CO_2

Both methods of calculation give essentially the same results within the limits of experimental error.

‡ The unusually high contents of ash, calcium and phosphorus raise the question of early osteopetrosis in this fetus. Histologic studies of the ribs showed them to be normal. Only well calcified bone was carefully dissected from the cartilage and analyzed. This may account for the high ash content.

§ Out of line with other results; hence suspect.

of our normal subjects varied only between 10.11 and 11.08 Gm. per hundred grams of bone, a difference of 0.87 Gm. per hundred grams of bone, or 0.86 per cent. The carbonate content of the bone increased with age from 2.38 per cent CO_2 in the fetus, to 3.37 per cent in the adult. As an index of the degree of mineralization of the bone, it is therefore possible to use the calcium, the phosphorus or the ash content of the dry fat-free bone, provided the samples are treated as described.

Residual Calcium-Phosphorus Ratio.—This is practically the same whether it is calculated on the assumption that the magnesium exists as magnesium carbonate or as tertiary magnesium phosphate. The results

8. Booher, L. E., and Hansmann, G. H.: J. Biol. Chem. **94**:195, 1931.

are so constant as to constitute a check on the analytic methods. We used a formula presented by Howland, Marriott and Kramer[9] and developed by Dr. Musselman to calculate the limit of error in this value, substituting the margin of error in our determinations of the calcium, phosphate, magnesium and carbonate contents. Thus the precision of our methods would give a value of 1.94 ± 0.027 for the residual calcium-phosphorus ratio. It is interesting to note that in the bone of only 1 subject, the 5½ hour old infant, did this ratio drop to significantly low levels: 1.89, 1.86 and 1.88. Furthermore, in the proximal and distal epiphyses of the tibia of our patient, where there

TABLE 2.—*Inorganic Composition of Normal and of Marble Bone: Tibia and Skull*

	Type of Bone					
	Tibia			Skull*		
	Fetus	Newborn Infant	Infant with Marble Bones	Fetus	Newborn Infant	Infant with Marble Bones
Age of subject	16-18 wk.	5½ hr.	4½ mo.	16-18 wk.	5½ hr.	4½ mo.
	Gm. in 100 Gm. of Bone					
Water	45.99	45.10	30.00	44.30	48.90	53.00
Fat	2.72	5.66	4.67	0.28	3.95	0.03
Analyses done on dry, defatted bone						
Ash	64.31	55.73	65.60 (Calculated)	62.76	53.14	54.40 (Calculated)
$\frac{\text{Residual Ca}}{\text{P}}$	1.93	1.86	1.96	1.92	1.96	1.94
(Assuming all magnesium bound to carbonate)						
$n = \frac{\text{⅓ residual Ca}}{\text{Ca combined with } CO_2}$	3.20	2.82	1.91	3.24	3.37	2.05

* The flat bones of the skull showed the least difference in ash content. The value of n was 2.05, as compared with 3.37 in the bones of the newly born infant. The histologic structure of the flat bones of the skull was typical of marble bones.

was histologic evidence of rickets and where healing had begun, the ratio was 1.72, indicating the existence of a compound here in which the calcium-phosphorus ratio approached that of secondary calcium phosphate. We have no proof, however, that secondary calcium phosphate was actually present. The samples were heated with strong hydrochloric acid, which brings about the hydrolytic cleavage of organic acid-soluble phosphorus to inorganic phosphorus, thereby decreasing the ratio of calcium to phosphorus in the solution. However, this could scarcely have been derived from cartilage, since the ratio of calcium to phosphorus in cartilage has been shown to be higher than in bone,[10] and we know

9. Howland, J.; Marriott, W. McK., and Kramer, B.: J. Biol. Chem. **68**: 721, 1926.

10. Logan, M.: J. Biol. Chem. **110**:375, 1935.

of no other source from which such large amounts of phosphorus might have been hydrolyzed.[11] The agreement between the calculated and the determined ash content of the costochondral junction of the ribs and the upper and lower epiphyses of the tibia unfortunately cannot be used either to verify or to disprove the existence of calcium acid phosphate ($CaHPO_4$), since the weight of tertiary calcium phosphate ($Ca_3[PO_4]_2$) and that of a mixture of calcium pyrophosphate ($Ca_2P_2O_7$) and calcium hydroxide ($Ca[OH]_2$) do not differ sufficiently for detection by such a crude method.[12]

TABLE 3.—*Inorganic Composition of Normal and of Marble Bone: Petrous Bone, Costochondral Junction and Epiphyses*

	Type of Bone				
	Petrous Bone			Costochondral Junction of Rib: Infant with Marble Bones	Upper and Lower Epiphyses and Cartilage of Tibia: Infant with Marble Bones
	Fetus	Newborn Infant	Infant with Marble Bones		
Age of subject	16-18 wk.	5½ hr.	4½ mo.	4½ mo.	4½ mo.
	Gm. in 100 Gm. of Bone				
Water	43.80	55.30	31.80	69.00	52.10
Fat	0.23	5.72	.....	5.91	2.58
Analyses of dry, defatted bone					
Ash	66.69	54.05	66.80	49.80	52.80
$\frac{\text{Residual Ca}}{\text{P}}$	1.94	1.88	1.95	1.94	1.72
(Assuming all magnesium bound to carbonate)					
$n = \frac{\text{½ residual calcium}}{\text{Ca combined with } CO_2}$	3.36	2.80	1.98	2.30	2.24

Neither does the method of calculating the acid-base balance aid in the solution of this question. However, as pointed out by Morgulis and Janecek,[13] the heating of calcium acid phosphate ($CaHPO_4$) at 500 C. converts it into calcium pyrophosphate ($Ca_2P_2O_7$), whereas, as shown in our own results, similar treatment of normal calcium orthophosphate ($Ca_3[PO_4]_2$) leaves the latter unchanged. Tertiary calcium

11. Such treatment would also convert pyrophosphate into orthophosphate.

12. The upper and lower epiphyses of the tibia, the same material which yielded the lowest ratio of calcium to inorganic phosphorus, i. e., 1.72, also showed an excess of acid equivalents over calcium and magnesium. Unfortunately, in this instance there was no determination of total base by the electrometric method, so that we were unable to demonstrate the presence of base other than calcium and magnesium.

13. Morgulis, S., and Janecek, E.: J. Biol. Chem. **93**:455, 1931.

14. Footnote deleted.

TABLE 4.—*Acid-Base Balance in Normal Bone* *

	Ribs				
	Fetus	Newborn Infant	Newborn Infant	Child	Adult
Age of subject	16-18 wk.	5½ hr.	6 days	10 yr.	20 yr.
Calcium	24.29	22.42	22.74	21.96	22.20
Phosphorus	11.90	11.08	10.59	10.27	10.11
Magnesium	0.51	0.42	0.32	0.36	0.26
Carbon dioxide	2.38	2.48	2.87	2.89	3.37
Phosphorus theoretically necessary for residual calcium and magnesium	11.84	10.76	10.65	10.30	10.12
Phosphorus actually found	11.90	11.08	10.59	10.27	10.11
Difference	0.06	0.32	0.06	0.03	0.01
Cc. of 0.1 N base equivalent to calcium and magnesium	12,540	11,534	11,610	11,255	11,292
Cc. of 0.1 N acid equivalent to phosphorus and carbon dioxide	12,591	11,843	11,543	11,245	11,310
Excess in cc. of 0.1 N base or acid	51	309	67	10	18
Percentage deviation	0.4	2.6	0.6	0.09	0.2
Actual ash	.....	.....	60.12	61.50	58.80
Calculated ash	.....	.....	59.42	57.70	58.10
Difference = Na + K as Cl,O=, expressed in percentage of dried fat-free bone	.....	.....	0.7	3.8	0.7
Total base determined electrometrically, equivalents per 100 Gm. of dried fat-free bone	.....	.....	.....	.....	1.148
Total base calculated by addition of Ca and Mg	.....	.....	.....	.....	1.130
Percentage of excess of undetermined base over total inorganic equivalents	.....	.....	.....	.....	0.8

* Unless otherwise indicated, values refer to number of grams per 100 Gm. of dry, fat-free bone.

TABLE 5.—*Inorganic Composition of Normal and of Marble Bone: Acid-Base Balance of Tibia and Skull* *

	Type of Bone					
	Tibia			Skull		
	Fetus	Newborn Infant	Infant with Marble Bones	Fetus	Newborn Infant	Infant with Marble Bones
Age of subject	16-18 wk.	5½ hr.	4½ mo.	16-18 wk.	5½ hr.	4½ mo.
Calcium	24.04	20.68	25.20	23.92	21.08	20.73
Phosphorus	11.78	10.29	11.22	11.75	10.12	9.52
Magnesium	0.52	0.34	0.36	0.45	0.40	0.34
Carbon dioxide	2.49	2.39	4.10	2.45	2.08	3.11
Phosphorus theoretically necessary for residual calcium and magnesium	11.65	9.84	11.37	11.58	10.24	9.49
Phosphorus actually found	11.78	10.29	11.22	11.75	10.12	9.52
Difference	0.07	0.45	0.15	0.17	0.12	0.03
Calcium and magnesium expressed as cc. of 0.1 N base	12,424	10,599	12,871	12,307	10,848	10,624
Phosphorus and carbon dioxide expressed as cc. of 0.1 N acid	12,524	11,037	12,714	12,476	10,732	10,620
Excess in cc. of 0.1 N base or acid	100	438	157	169	116	4
Percentage of deviation	0.8	4.0	1.2	1.3	1.1	0.04
Actual ash	64.31	55.73				
Calculated ash	64.17	54.86				
Difference = Na + K as Cl,O=, expressed in percentage of dried fat-free bone	0.14	0.87				
Total base determined electrometrically, equivalents per 100 Gm. of dried fat-free bone	1.257	1.147				
Total base calculated by addition of calcium and magnesium	1.242	1.059				
Percentage undetermined (Na + K) of total number of inorganic equivalents	0.6	3.0				

* Unless otherwise indicated, values refer to grams per 100 Gm. of bone.

phosphate on being heated in water or in weak acid or after long standing hydrolyzed so that the phosphorus could be determined as orthophosphate, whereas monohydric calcium orthophosphate ($CaHPO_4$) after conversion by heating into calcium pyrophosphate ($Ca_2P_2O_7$) could be determined only after prolonged hydrolysis with strong mineral acid. A discrepancy between the inorganic phosphorus in unashed and in ashed bone would suggest the presence in the original bone powder of a

TABLE 6.—*Inorganic Composition of Normal and of Marble Bone: Acid-Base Balance of Petrous Bone, Costochondral Junction and Epiphyses*

	Type of Bone				
	Petrous			Costochondral Junction of Ribs:	Upper and Lower Epiphyses and Cartilage of Tibia:
	Fetus	Newborn Infant	Infant with Marble Bones	Infant with Marble Bones	Infant with Marble Bones
Age of subject	16-18 wk.	5½ hr.	4½ mo.	4½ mo.	4½ mo.
Calcium	25.70	20.82	24.46	16.98	18.23
Phosphorus	12.73	10.47	11.22	7.82	9.60
Magnesium	0.72	0.57	0.58	0.19	0.37
Carbon dioxide	2.55	2.43	3.87	2.36	2.59
Phosphorus theoretically necessary for residual calcium and magnesium	12.67	10.09	11.30	7.81	8.51
Phosphorus actually found	12.73	10.47	11.22	7.82	9.60
Difference	0.06	0.38	0.08	0.01	1.09
Cc. of 0.1 N base equivalent to calcium and magnesium	13,416	10,858	12,406	8,629	9,402
Cc. of 0.1 N acid equivalent to phosphorus and carbon dioxide	13,471	11,233	12,609	8,635	10,462
Excess in cc. of 0.1 N base or acid	55	375	203	6	1,060
Percentage of deviation	0.4	3.4	1.6	0.08	10.0
Actual ash	.....	.....	66.80	49.80	52.80
Calculated ash	.....	.....	64.70	44.30	51.60
Difference = Na + K as $Cl,O^=$, expressed in percentage of dried fat-free bone	.....	.....	2.1	5.5	2
Total base determined electrometrically, equivalents per 100 Gm. of dried fat-free bone	.....	1.112			
Total base calculated by addition of Ca and Mg	.....	1.088			
Percentage undetermined (Na + K) of total number of inorganic equivalents	.....	1.1			

* Unless otherwise indicated, values refer to grams per 100 Gm. of bone.

phosphorus compound less resistant to heat than tertiary calcium phosphate. This we realize is an indirect approach to a problem which could be more directly solved by roentgen analyses of the crystals.

Value of n.—The value of *n* has been used by Bogert and Hastings [15] to indicate the molecular ratio of tertiary phosphate to calcium carbonate. Howland, Marriott and Kramer showed that this ratio is lower in the rachitic bone than in normal bone, and Kramer and Shear [16] showed that it decreases with age, the amount of calcium car-

15. Bogert, L., and Hastings, A. B.: J. Biol. Chem. **94**:473, 1931.

16. Kramer, B., and Shear, M. J.: J. Biol. Chem. **79**:147, 1928.

bonate being higher in bones of adults than in bones of infants and children. In table 1 there is a striking confirmation of this fact, the value of n decreasing with increasing age from the fetal period to the age of 24 years, being equal to 3.39 in the fetus and 2.08 in the 24 year old adult. This condition obtains regardless of which bone is compared. It is worthy of note that the value of n for marble bones is similar to that obtained for adult bones. Only in the costochondral junctions of the ribs and at the upper and lower epiphyses of the tibia does the value of n approach that found for the bones in infancy.

Acid-Base Balance in Bone.—When bone is analyzed with reference to acids and bases there is a slight excess of either acids or base varying

TABLE 7.—*Data on Subjects Whose Bones Were Analyzed*

Name	Age	Sex	Diagnosis
R. E.	16-18 wk.	.....	Miscarriage; no congenital abnormalities
F. C.	5½ hr.	Male	Atelectasis of lungs
M. O.	6 days	Female	Clinical diagnosis: congenital atresia of esophagus, bronchopneumonia Anatomic diagnosis: atresia of esophagus with esophagotracheal fistula, acute bronchiolitis, bilateral focal pneumonia
R. W.	10 yr.	Female	Clinical diagnosis: atypical verrucous endocarditis, chronic nephritis, hypertension Anatomic diagnosis: healed mitral, aortic and mural endocarditis, scars of myocardium, cardiac hypertrophy, chronic and acute nephritis, anasarca, focal pneumonia, otitis media
A. M.	29 yr.	Male	Clinical diagnosis: malignant nephrosclerosis, uremia, hypertension and arteriosclerosis, enlarged heart, coronary sclerosis, myocardial fibrosis, pericarditis, heart failure, anasarca Anatomic diagnosis: sclerosis of renal vessels, scars of kidneys, cardiac hypertrophy and dilation, pericarditis, hemorrhagic organizing passive congestion of viscera, hydrothorax, edema of lower extremities, edema of brain, focal pneumonia
R. H.	4½ mo.	Male	Marble bones; rickets (scurvy ?)

from 0.4 to 4 per cent in normal bones and from 0.4 to 1.6 per cent in our case of marble bones. However, a comparison of values of total base, determined electrometrically, with those obtained by the analysis of calcium and magnesium showed a greater base content by the electrometric method which varied between 0.6 and 3 per cent and 2.1 per cent for the petrous bone of our patient. This is probably due to other bases, such as sodium and potassium, in both types of bone. There is obviously therefore a small quantity of base present in bone other than calcium and magnesium, and it is also likely that the same holds true for acids.

COMMENT

The mechanism of calcification is a subject of universal interest. Deposition of calcium salts is a widespread biologic phenomenon and also occurs in many pathologic states. In its early stages, at least, the mecha-

nism is one of precipitation of an insoluble salt from a saturated or supersaturated solution of bone-forming elements. Local factors, including the biologic activity of the cell itself, undoubtedly play a role, since otherwise deposition would be universal rather than selective in its localization. A study of the equilibrium between the solid phase, such as the inorganic matter of bone, and the supernatant fluid, that is, the circulating tissue fluid, must of necessity begin with exact knowledge of the chemical composition and the crystal structure of the solid phase. In the past, methods of study of this solid phase have been chiefly chemical. Within the last few years ingenious physical methods have been introduced, and these have yielded more direct evidence regarding the structure of this inorganic material. The earlier idea of Gassmann and the somewhat more recent Werner concept [17] were that the solid phase consists of a compound in which calcium, inorganic phosphorus and carbonate exist in a definite stoichiometric relationship. These are no longer tenable in the light of evidence of the changing value of the molecular ratio of calcium phosphate to calcium carbonate with age and with disease. Recent work has shown a difference in this ratio even between the outer and the inner layer of the same bone. This difference may be exaggerated by diet. Two additional hypotheses have been advanced: (1) that the early calcification differs in its composition from mature bony material, i. e., that secondary calcium phosphate constitutes the initial precipitate, which is quickly converted into the tertiary salt, and (2) that tertiary phosphate is deposited and later adsorbs calcium carbonate ($CaCO_3$) or calcium carbonate and magnesium carbonate ($MgCO_3$). Other authors have maintained that a crystal dahlite, of the apatite series, is deposited, in which normal calcium orthophosphate ($Ca_3[PO_4]_2$) is the first component, together with another calcium salt with a variable anion, such as OH, F, Co_3 or Cl_2. The arguments against the first assumption have been summarized by Huggins and critically discussed by Logan. Suffice it to say that although in 1 instance primary calcification was shown to be different in its composition from mature bone, the difference was not such as to indicate the existence of secondary calcium phosphate. Other analysts have also failed to detect the presence of secondary calcium phosphate. It is worthy of note that when the epiphysial end of the bone of our patient was analyzed, the ratio of calcium to phosphorus was found to be distinctly below that required to form tertiary calcium phosphate. The possibility that a mixture of tertiary and secondary calcium phosphate was present suggests itself as one explanation. Other explanations are possible. To account for a ratio of 1.72, about one third of

17. Gassmann, T.: Ztschr. f. physiol. Chem. **70**:161, 1910; **90**:250, 1914.

the phosphorus would have to be in the form of secondary calcium phosphate, an amount readily detectable by roentgen analysis. Such determinations were not made. The derivation of inorganic phosphorus from an organic compound by acid hydrolysis has been suggested. Cartilage is richer in calcium than in phosphorus, so that an admixture of cartilage should alter the ratio in the opposite direction. The matter deserves further investigation.

The existence of a compound of the hydroxyapatite type has been suggested because of the finding at times in an area of fresh calcification of a residual calcium-phosphorus ratio greater than 1.94 and the demonstration of a measurable excess of base due to calcium. Our results failed to demonstrate such an excess, while in most instances the residual calcium-phosphorus ratio corresponded exactly with that of normal calcium orthophosphate ($Ca_3[PO_4]_2$). The hydroxyapatite hypothesis of Morgulis was discussed by Marek, Wellman and Urbányi,[18] and his findings were interpreted as resulting from the hydrolysis of tertiary calcium phosphate during the analysis.

Roentgen spectrography has revealed that the inorganic material of bone has a crystalline structure identical with that of a crystal of the apatite group, dahlite; that is, that the salt consists of tertiary calcium phosphate and another compound (calcium x) in which the x may represent such a substance as oxygen, carbonate, hydroxide, fluoride or chloride, i. e., $n[Ca_3(PO_4)_2]Ca(OH)_2.CaCO_3$ or $n[Ca_3(PO_4)_2]CaCO_3$.

Using this method of roentgen spectography, de Jong,[19] Roseberry, Hastings and Morse[20] and Taylor and Sheard[21] were unable to detect the presence of secondary calcium phosphate in normal bone. They found lines corresponding with those of tertiary calcium phosphate. However, they were also unable to obtain evidence of the existence of calcium carbonate, which according to chemical data must be present. An explanation of this anomalous situation in bone was offered by Logan and Taylor,[22] who pointed out that Walden and Cohen[23] have shown that adsorbed materials do not affect the roentgen spectrum while liquid crystals disperse the rays only slightly. Hence, if calcium carbonate is adsorbed on the crystal of tertiary calcium phosphate, or if

18. Marek, J.; Wellman, O., and Urbányi, L.: Ztschr. f. physiol. Chem. **226**:3, 1934.

19. de Jong, W. F.: Rec. trav. chim. d. Pays-Bas **45**:455, 1926.

20. Roseberry, H. H.; Hastings, A. B., and Morse, J. K.: J. Biol. Chem. **90**: 395, 1931.

21. Taylor, N. W., and Sheard, C.: J. Biol. Chem. **81**:479, 1929.

22. Logan, M., and Taylor, H.: J. Biol. Chem. **119**:293, 1937.

23. Walden, G. H., Jr., and Cohen, M. V.: J. Am. Chem. Soc. **57**:2591, 1935.

secondary calcium phosphate exists as liquid crystals in a fluid bathing the newly calcified cartilage or in the water of hydration of normal calcium orthophosphate ($Ca_3[PO_4]_2$) roentgen spectrography would fail to reveal the presence of these substances. However, such a large amount of secondary calcium phosphate as was presumably present in the tibial epiphyses in our case of osteopetrosis should, however, be demonstrable by roentgen analysis.

Four possible explanations may be suggested for the low molar ratio of calcium phosphate to calcium carbonate found in our case: (1) that it was due to the accompanying rickets, since histologically the bones showed a severe degree of rickets; (2) that such a ratio is characteristic of this disease; (3) that it was merely the result of the prevailing concentration of calcium, inorganic phosphorus and carbonate in the blood, or (4) that it was due to diet.[24]

As for the first two suggestions, it is doubtful whether the rachitic process could account for the low value of n, since the major part of the material analyzed came from the diaphysis, where the rachitic process was minimal. It has been suggested that in marble bones the bony material represents a primitive and imperfect type of osseous structure. Chemical analysis indicates that the inorganic material in its composition resembles more nearly that of adult bone. It is likely that the peculiar composition of the bone is a result of the abnormal composition of the blood serum with reference to the bone-forming elements calcium, phosphorus and carbonate. In the rachitic rat, when the phosphorus is maintained at a low level, the carbonate and the calcium level being normal, and when this equilibrium is maintained over the entire experimental period, the value of n is identical with the value obtained for marble bones, although the histologic appearance of the bone is different. The relation of the composition of bone to that of blood deserves further investigation. In the absence of sufficient amounts of vitamin D, the ash content and the calcium-phosphorus ratio of the bones of animals are determined by both the absolute amounts and the proportions of calcium to phosphorus in the diet. This relationship of bone composition to blood composition in infants is a wholly unexplored field.

The analyses of the bones of our patient reveal a residual calcium-phosphorus ratio which indicates that the chief phosphorus compound is tertiary calcium phosphate, the bone in that respect being identical in composition with normal bone. However, the value of n is close to 2, varying from 1.91 in the tibia to 1.98 in the petrous

24. Bethke, R. M.; Kick, C. H., and Wilder, O. H.: J. Biol. Chem. **98**:389, 1932.

bone and 2.05 in the flat bones of the skull. In this respect the bone resembles mature adult bone or rachitic bone, both of which contain a higher percentage of calcium carbonate than do the bones of the normal infant. Our patient maintained a low concentration of both calcium and phosphorus in the serum, with a normal bicarbonate level, in spite of the usual infant's diet and therapeutic doses of vitamin D. We therefore believe that the high ash content and the low value of n are characteristic of this disease, since in the normal infant a similar dietary regimen would have produced normal blood calcium and phosphorus levels and normal bone. The severe rickets which this infant had indicates perhaps an increased susceptibility to rickets of infants suffering with marble bones, probably due to failure readily to utilize vitamin D administered orally. A similar study in a case of osteopetrosis uncomplicated by rickets would supply the answer to our question as to the presence of this finding in cases of uncomplicated marble bones. The flat bones of the skull showed no hypermineralization, although histologically the lesion was characteristic of marble bones. The value of n, however, was approximately 2. In the last analysis, we are inclined to the belief that the rachitic factor was so severe that it overshadowed all the other lesions and hence gave a chemical picture identical with that of rickets. Hypermineralization, however, was maintained in some bones in spite of the demineralizing effect of the rachitic process.

SUMMARY AND CONCLUSIONS

The percentage of ash, of calcium and of phosphorus in the bones of an infant with osteopetrosis, where the characteristic lesion was present, was distinctly higher than in the corresponding bones of a normal newly born infant, except in the flat bones of the skull.

The ratio of residual calcium to phosphorus was in harmony with the idea that the calcium-phosphorus compound in marble bones is tertiary calcium phosphate.

In analyses of the upper and lower tibial epiphyses, evidence of a calcium-phosphorus compound having a lower ratio of calcium to phosphorus was obtained.

When calculated in terms of acid-base equivalents, the total fixed base content as determined by electrodialysis exceeded the sum of the calcium and the magnesium content by 1.2 to 5.9 per cent. Part of this excess of base undoubtedly was represented by the sodium and potassium content of the bone. There is therefore no major basic component in marble bones which is not represented by the well known elements calcium, magnesium, sodium and potassium.

The value of n, i. e., the molecular ratio of calcium phosphate to calcium carbonate in the bones of the infant with osteopetrosis, was

found to be approximately 2, corresponding to that found in normal adult bone or in the bones of rachitic infants, i. e., has more carbonate than bones of normal infants of the same age.

There was a satisfactory agreement between the ash content as determined by heating dried fat-free bone at 500 C. and the ash content calculated on the assumption that calcium and magnesium exist as carbonates and that phosphorus is present as tertiary calcium phosphate. On the same assumption, determinations of the acid-base balance showed a slightly positive base balance.

The significant findings therefore are a high carbonate content and hypermineralization. A high carbonate content is also present in adult and rachitic bone and may account for the increased fragility. Hypermineralization is a finding inconsistent with the diagnosis of rickets. It is therefore likely that the combination of high carbonate content and hypermineralization characterizes the mineral content of marble bones.

LIMITATION OF BACTERIAL CONTAMINATION OF AIR BY A NEW AUTOMATIC INCUBATOR FOR INFANTS

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A new, automatically controlled incubator for premature infants, supplied by air from out-of-doors, has afforded the opportunity of studying the effect of such a chamber on bacterial contamination of the air breathed by the infants. The incubator has been previously described.[1]

It is the purpose of the present report to discuss bacterial counts made on the air within the incubator, the air from out-of-doors and the air in different wards in which the incubators were placed, as well as the apparent effect of the reduction in bacteria on infant morbidity and mortality.

Extreme susceptibility to infection is inherent in premature infants. In spite of rigid nursery technic they become infected with discouraging facility. Usually the respiratory tract is attacked first, although the low resistance of the premature infant is not limited to this one system. Infection may begin elsewhere, as in the gastrointestinal tract or the skin, in the presence of specific epidemics or as the result of direct contact with a contaminated article.

Infections of the respiratory tract are acquired chiefly from two sources: first, actual contact with those in attendance or with the droplets of moisture expelled by them and, second, aspiration of the dried residue of such droplets floating in the air. The wearing of gown and mask by the attendant is inadequate for the infant's protection from either source, as masks of gauze or other material which permit the passage of air for breathing intercept only the relatively large droplets. Those droplets which are not enmeshed are free either to

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This study was supported in part by a grant from the Commonwealth Fund to the University of Pennsylvania for investigations on air-borne infections.

1. Chapple, C. C.: An Incubator for Infants, Am. J. Obst. & Gynec. **35**:1062, 1938.

carry their attached organisms directly to the patient or to evaporate and float in the air as "droplet nuclei." [2] These floating "nuclei," as well as those carried from other parts of the hospital, may reach the infants and be inhaled by them. That the bacteria entering the air from the nasopharynx do not die immediately but remain in the air long enough to be transmitted to other persons in the same room or building has been demonstrated by Wells,[3] who has shown that Pneumococcus type 1, Bacillus diphtheriae, Streptococcus haemolyticus and Streptococcus viridans survive for forty-eight hours after artificial atomization into the air. Bacteria which become attached to dust particles settle out in a shorter time and can be recovered in Petri dishes set on the floor, as can those which are carried directly to Petri dishes by air currents. The bacteria remaining suspended, though not readily demonstrable by the Petri dish technic, may be detected by a method devised by Wells [4] for the culture of "air-borne" bacteria, to be described.

To protect the premature infant against this source of infection as well as against actual contact and droplet infection, an incubator was devised which can be kept tightly closed at all times.[1] Into its sealed chamber air is drawn from out-of-doors after being filtered to remove dust particles and is then heated and humidified to any level selected for the infant's need. In the incubator the temperature can be maintained with less than a degree of fluctuation and the relative humidity within 5 per cent. The infant is handled through air-tight sleeves, bottles and diapers being supplied through an air lock. Within the chamber is a bed and a scales.

In order to prevent leakage of air from the ward into the incubator a slightly increased positive pressure is maintained in the chamber, so that the flow of air is from inside the incubator toward the room instead of in the reverse direction, i. e., toward the baby. As only the hands come into contact with the infant, gowns and masks are not necessary. The hands are washed before their insertion into the sleeves, but no other precautions need be taken even though the machine is being used in a ward for patients with infectious diseases.

The advantages of such an apparatus are evident. The babies are left naked and so are unhampered in their movements of respiration and exercise. Their handling is vastly simplified. The optimal temperature and humidity for each infant can be maintained without affecting the atmosphere in which the nurse must work. As the chamber is air

2. Wells, W. F.: Droplets and Droplet Nuclei, Am. J. Hyg. **20**:611, 1934.

3. Wells, W. F., and Stone, W. R.: Viability of Droplet Nuclei, Am. J. Hyg. **20**:619, 1934.

4. Wells, W. F.; Phelps, E. B., and Winslow, C. E.: Report of Sub-Committee on Bacteriological Procedures in Air Analysis, Am. J. Pub. Health (supp.) **27**:97, 1937.

tight, high oygen concentration for extended periods is possible. Contact infection is minimized and air-borne contamination practically excluded.

Since the air was drawn from out-of-doors and the incubators were operated in the wards, it became important to determine the actual number of bacteria in the air of the incubator, in the outdoor air and in the air from the wards in which the incubators were used. In carrying out this investigation the technic of Wells was employed. The Wells apparatus is a centrifugal machine so constructed that a culture tube placed inside is rotated on its vertical axis. A warm culture medium with an agar base is poured into the tube at the beginning of each sampling. The spinning motion distributes the medium in a thin layer over the inner surface of the tube, where it solidifies as the agar cools. Simultaneously air is drawn into the culture tube, where the centrifugal action applies it forcibly to the agar surface, to which the bacteria adhere. Thus it recovers from the air both the dust-borne bacteria which are ordinarily collected on Petri dishes and the air-borne bacteria which are too light to collect on such dishes by gravity.

The centrifuge is designed to draw in 1 cubic foot (28,300 cc.) of air per minute, and in this study it was rotated for five minute periods in all instances, so that each sample represents the bacteria found in 5 cubic feet (141,500 cc.) of air. The medium used for the culture tubes was composed of 3 per cent veal brain agar enriched by the addition of 7 drops of citrated human blood to each 20 cc. of culture medium.

After a tube had been exposed in the manner described it was removed from the centrifuge and incubated for forty-eight hours. The bacterial colonies on the culture surface were counted. The counting was done by the naked eye or with the assistance of a binocular dissecting microscope, depending on the extent of contamination.[4a]

The determinations on ward air were made in the infants' wards of the Children's Hospital of Philadelphia. Each ward contained 15 infants in individual cubicles enclosing a bed, a bedside stand, a chair, a wash-basin with running water and a rack for the attendant's gown. Walls on the sides and backs of the cubicles started 1 foot (30 cm.) from the floor and extended upward for 6 feet (180 cm.), to within 4 feet (120 cm.) of the ceiling. This construction allowed circulation of air about the ward but established a barrier to contact infection between infants.

Representative samplings of air were made with the centrifuge intake at 2 feet (60 cm.) above floor level in various cubicles throughout the

4a. Miss Ruth Blumfeld, of the Laboratory of Sanitary Ventilation, University of Pennsylvania School of Medicine, did the counting and the isolating and identifying of the streptococci.

wards. The operation of the machine was discontinued during sweeping and window cleaning in order to avoid sampling of air temporarily overladen with dust. Samples of outdoor air were taken either by placing the machine itself on the adjacent sun porch or by passing a 36 inch (90 cm.) hose, attached to the centrifuge, through a window. The air from the incubator was sampled by passing the tube into the incubator cabinet through the connecting-plug opening in the top.

All colonies of organisms resembling Str. viridans were transferred to blood agar plates and then to broth and to various sugars for identification. Wells and Wells [5] have confirmed Gordon's observation that the frequency of this organism constitutes an index of the extent to which air is infected by the human nasopharynx.

The results obtained from air in the wards are outlined in table 1. The average of counts taken for a period of two months was 523 colo-

TABLE 1.—*Bacterial Counts of Air in the Pediatric Ward*

Date	Number of Samples	Average Number of Colonies per 5 Cubic Feet	Average Number of Colonies of Str. Viridans per 5 Cubic Feet
3/31/38	5	462	0.60
4/11/38	6	302	1.33
4/13/38	4	428	0.50
4/14/38	5	1,031	0.60
4/20/38	9	379	2.33
4/21/38	10	606	2.00
4/27/38	15	502	0.80
5/ 5/38	14	294	0.86
5/10/38	18	682	3.72
5/14/38	8	584	0.62
5/16/38	9	545	2.55
Total number of samples from 3/31/38 to 5/16/38			103
Average number of colonies per 5 cubic feet of air			523
Average number of colonies of Str. viridans per 5 cubic feet of air			1.7

nies per 5 cubic feet of air. Colonies of Str. viridans had an average of 1.7 per 5 cubic feet. Although these figures may not appear significant, if they are translated into the number of organisms inhaled during twenty-four hours it is seen that the occupant of the ward would be inhaling a great number of organisms, indicative of potential hazard. Assuming the minute tidal volume of a 3 pound 5 ounce (1,499 Gm.) infant to be in the vicinity of 300 cc., he would inhale approximately 15 cubic feet (424,500 cc.) of air during a twenty-four hour period. In an environment such as we have studied this would represent an inhalation of the number of bacteria capable of producing approximately 1,500 colonies on blood agar medium as described. Of these, one would expect a total of about five colonies of Str. viridans, as well as pathogenic organisms which, while not identified on the tubes, might

5. Wells, W. F., and Wells, M. W.: Air-Borne Infection, J. A. M. A. **107**: 1698 (Nov. 21) 1936.

similarly circulate in the air. For a normal newborn infant these figures would be approximately doubled.

A short series of experiments in two other Philadelphia hospitals showed similar conditions. In the wards for newborn children of both institutions Str. viridans was recovered although rigid isolation technic was carried out. The total bacterial counts were smaller in view of the complete isolation of the wards from the usual sources of contamination, yet Str. viridans was found in most of the cultures.

It should be borne in mind also that the majority of samples of air were taken at a time when the height of the "respiratory disease season" had passed. In addition, during the months of April and May the wards

TABLE 2.—*Bacterial Counts of Outdoor Air*

Date	Number of Samples	Number of Colonies per 5 Cubic Feet of Air	Date	Number of Samples	Number of Colonies per 5 Cubic Feet of Air
4/13/38	3	36	4/25/38	4	38
4/14/38	4	25	5/ 2/38	5	12
4/19/38	2	23	5/28/38	5	12

Total number of samples taken..... 23
Average number of colonies per 5 cubic feet of air..... 25
No colonies of Str. viridans were found. The colonies were largely sarcinas

TABLE 3.—*Bacterial Counts of Incubator Air*

Date	Number of Samples	Number of Colonies per 5 Cubic Feet of Air	Date	Number of Samples	Number of Colonies per 5 Cubic Feet of Air
4/13/38	5	4	5/ 2/38	14	16
4/14/38	8	20	5/ 3/38	14	16
4/19/38	7	14	5/11/38	18	7
4/25/38	13	12	5/28/38	13	39

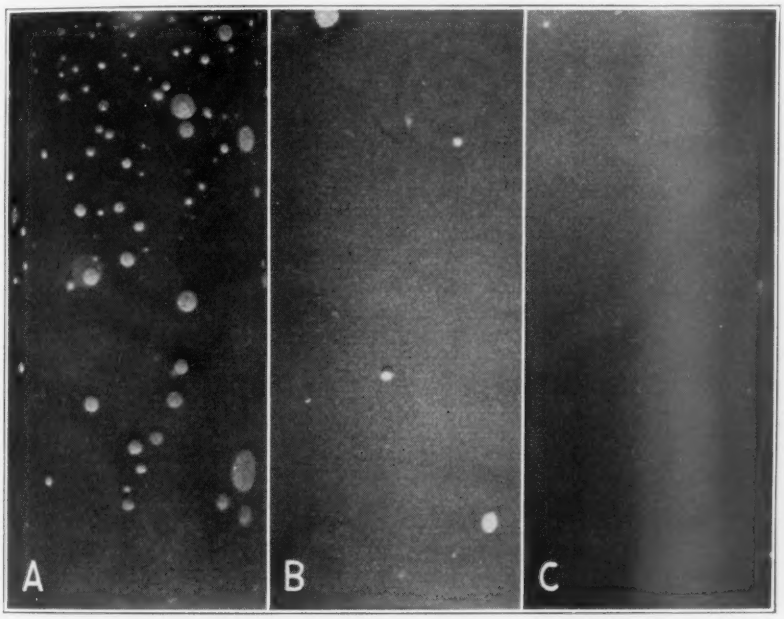
Total number of samples taken..... 92
Average number of colonies per 5 cubic feet of air..... 18
No colonies of Str. viridans were found. The cultures were largely sarcinas

were freely ventilated with outdoor air, so that the ventilation was greatly increased in comparison to that existent during the winter months, when infections of the respiratory tract were more frequent. Had these studies been carried out during December, January, February and March, one can assume that a greater gross contamination as well as an increased number of Str. viridans would have been found.

In table 2 are listed the results of samplings of outdoor air. The difference between the counts of ward and of outdoor air is obvious, even though the latter represents air found within a few feet of the hospital, which is located in a congested district of Philadelphia.

Table 3 gives the results of samplings made of air in the incubators. These figures compare favorably with those found for outdoor air and are markedly lower than the counts in the air of the wards in which the

incubators were used. It is worth noting that the bacterial counts on ward air were approximately twenty-six times the bacterial counts on air from the incubator, and it is also significant that the few organisms found in the incubator air were mostly sarcinas brought in by the outdoor air (see illustration). Str. viridans was not found in the air of the incubator in any of the samples taken at the Children's Hospital. The one sample on which a colony was found was taken in a maternity hospital immediately after a bottle and a diaper had been passed through the air lock. The bacterial counts of the air obtained when the incubator was occupied by an infant have been compared with those obtained



Photographs of cultures obtained in the Wells air centrifuge. *A*, culture from air of the pediatric ward (523 colonies per 5 cubic feet); *B*, culture from outdoor air (25 colonies per 5 cubic feet); *C*, culture from air in the incubator (18 colonies per 5 cubic feet).

when it was empty, under the same conditions of temperature and humidity, and have shown no significant difference. Routine care of the child in the cabinet necessitates the occasional insertion of the attendant's arms through the sleeves of the portholes, but this procedure has been found to result in no increase in the bacterial contamination (table 4). However, the administration of feedings and the changing of diapers necessitate the passage through the air lock of the materials essential to these procedures. Momentarily there is a small increase in the count as a result of this slight contamination with ward air. Despite

the fact that this unavoidable increase becomes manifest in the culture taken at this time, within less than five minutes the previous low value is restored (table 4).

It is to be expected that the low bacterial count in the incubator air, plus the minimization of contact, would be reflected in the morbidity and mortality rates for infants in the incubator. This appears to be the case.

One group of 10 premature infants was cared for in a nursery set aside for that purpose. In this room the nurse wore a gown and mask at all times and all other persons were excluded except the staff physi-

TABLE 4.—*Bacterial Counts Obtained During Routine Maneuvers*

Tube	Time	Colonies per 5 Cubic Feet	Streptococcus Viridans Colonies per 5 Cubic Feet	Comment
			Samples of Incubator Air	
1	1:04	8	0	Nurse inserts arms through sleeves
2	1:10	6	0	
3	1:19	14	0	
4	1:27	9	0	
5	1:34	8	0	
6	1:48	38	1	Feeding materials inserted through air-lock; feeding completely administered during this five minute period
7	1:53	14	0	
			Samples of Nursery Air	
8	2:07	102	0	
9	2:12	97	3	
10	2:18	110	3	
11	2:26	51	1	
			Samples of Outdoor Air	
12	2:43	33	0	
13	2:48	13	0	

The incubator housed a newborn infant in a ward of a maternity nursery containing 15 infants. The single window of the room was open 10 inches (25 cm.) from the bottom. The day was warm and clear. The room temperature was 79 F.; the incubator temperature, 90 F.; the relative humidity, 70 per cent.

cians, who made only necessary visits. Another group of 10 premature infants was cared for in the incubators in an open ward. In this ward cross infection was occurring constantly but the nurses attending the incubators wore neither masks nor gowns. They were required only to wash their hands before handling a baby. Selection of infants for the two groups was not attempted except that, when possible, the smaller babies were placed in the incubator. No infant was considered to be premature who weighed more than 4½ pounds (2,040 Gm.), and there was only 1 of this size. The smallest weighed 25 ounces (708 Gm.); another weighed 31 ounces (879 Gm.), and several weighed between 36 and 40 ounces (1,021 to 1,134 Gm.), or approximately 2½ pounds.

Of the babies in the special ward for premature infants, 4 died of pneumonia and 1 of diarrhea. In the incubators none of the infants

had an infection of the respiratory tract, and only 1 had diarrhea. The diarrhea was mild and transient. A single death occurred, which was due to staphylococcic septicemia originating in an abscess at the site of repeated hypodermoclyses. In a word, then, the mortality in the ward for premature infants was 50 per cent, most of the deaths being due to infections of the respiratory tract; the mortality of the incubator group was 10 per cent, and the morbidity of the latter group, with the exception of the case of septicemia, was practically nil. Although the small number of infants studied in these two groups does not warrant conclusive statements, the evidence obtained greatly favors the incubator.

Additionally, there have been approximately 30 infants in such incubators in other hospitals. The babies in them have been entirely free of infection, with 2 exceptions. The first of the infected infants had erysipelas, which was probably contracted on direct contact, as it was in a pediatric ward. This infant recovered. The second, a mongolian idiot, had the only infection of the respiratory tract recorded for the group of infants cared for in the incubator, otitis media. The organism involved was not determined, as drainage was present for a very short time before recovery.

It is probable that these results cannot be ascribed to the low bacterial content alone, as the environmental conditions doubtless have some beneficial effect on resistance to infection. In the incubator the infants' rectal temperature was held ordinarily within 0.4 degree (F.) diurnal fluctuation. The relative humidity in the incubator air was kept at a high level, as recommended by Blackfan and Yaglou.[6] Also, in the case of the infants weighing less than 3½ pounds (1,530 Gm.) oxygen was added routinely to the chamber to maintain 25 to 46 per cent oxygen concentration, depending on the size and the needs of the baby. Under these conditions cyanotic attacks were practically nonexistent. It would appear then that in an environment such as it is practicable to maintain in this incubator the infant's energy reserves are spared and his resistance to infection is proportionately enhanced.

SUMMARY

The bacterial pollution of air in the wards of a children's hospital has been demonstrated by means of an air centrifuge. The bacterial counts obtained show the extent of total bacterial contamination and also of contamination with Str. viridans, which is considered an index of the pollution of the air by the human nasopharynx. The potential danger of infected air has been pointed out. An incubator has been

6. Blackfan, K. D., and Yaglou, C. P.: The Premature Infant: Effects of Atmospheric Conditions on Growth and Development, Am. J. Dis. Child. **46**:1175 (Nov., pt. 2) 1933.

described which is devised in such a manner as to protect the premature infant from most of the hazards of immediate contact and from virtually all of the hazards of indirect contact. In the incubator the atmospheric environment, which is under automatic control, is maintained so constant that the infants are left naked, and individual requirements, including high oxygen concentration, can be met for each infant. The bacterial content of the incubator air is as little as that of air from outdoors and is less than the air of the ward in which the incubator is placed. By means of this incubator the mortality and morbidity rates of premature infants appear to have been substantially reduced.

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PLACENTAL TRANSMISSION OF HYPERSENSITIVENESS TO ASCARIS LUMBRICOIDES ACTIVELY INDUCED IN THE PREGNANT WOMAN

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Ratner, Jackson and Gruehl [1] conclusively demonstrated intrauterine sensitization of the fetus of the guinea pig. They actively sensitized females with horse serum, and when these animals were bred with normal males, all of the offspring showed sensitivity to horse serum. This passive transmission of hypersensitiveness lasted from two and one-half to four months. Subsequently, Cohen and Woodruff [2] confirmed these findings with guinea pigs, using egg white as the sensitizing antigen. The passively sensitized offspring were bred at from 3 to 6 months of age. About 50 per cent of the animals born of these matings showed sensitivity. Transmission of hypersensitiveness could not be demonstrated beyond this stage.

Ratner [3] presented 15 cases of food allergy in children. In each of these cases the author stated that in the antepartum period the mother consumed unusually large amounts of certain foods and that some time after birth the offspring showed sensitivity to the same foods. On the basis of these findings, the experimental evidence of intrauterine sensitization in the guinea pig and the similarity between the placenta in man and that in the guinea pig in that a single cell layer separates the fetal from the maternal circulation, Ratner concluded that sensitivity in the human being could similarly be induced in utero, either actively or passively. Tuft,[4] Smythe,[5] Walzer [6] and other workers have taken

From the Allergy Clinic of the Beth Moses Hospital.

1. Ratner, B.; Jackson, H. C., and Gruehl, H. E.: Transmission of Protein Hypersensitiveness from Mother to Offspring, J. Immunol. **14**:291, 1927.

2. Cohen, M. B., and Woodruff, B. P.: Observations on Transmission of Anaphylactic Sensitivity in the Guinea Pig, J. Allergy **8**:437, 1937.

3. Ratner, B.: Possible Causal Factor of Food Allergy in Certain Infants, Am. J. Dis. Child. **36**:277 (Aug.) 1928.

4. Tuft, L.: Clinical Allergy, Philadelphia, W. B. Saunders Company, 1937, pp. 48 and 123.

5. Smythe, F. S.: Allergic Diseases in Childhood: Review of the Literature, J. Allergy **8**:89, 1936.

6. Walzer, M.: Critical Review of Recent Literature on Physical Allergy: Intrauterine Sensitization, Mechanism of Specific Treatment in Hay Fever; Sensitiveness in Monkeys, J. Allergy **9**:64, 1937.

exception to this point of view. Experimentally Bell and Eriksson[7] were unable to demonstrate any transmission of sensitivity from the sensitive mother to the offspring. They studied 10 pregnant women, of whom 5 were sensitive to a pollen and 5 to feathers, goat epithelium, orange and spinach. These women on direct testing manifested positive reactions to these allergens, and reagins for these substances could be demonstrated in the serum. Studies of the serum obtained from the fetal cord, however, failed to reveal the presence of any of the skin-sensitizing antibodies which were present in the maternal blood. Direct cutaneous tests on the newborn gave unsatisfactory results. Other investigators, including Walzer[8] and Caulfeild,[9] confirmed the findings of Bell.

One of the chief differences between anaphylaxis and atopy, as has been pointed out by Coca and his co-workers,[10] is the ease with which one can experimentally induce anaphylaxis in the laboratory animal as compared with the great difficulty one encounters in actively sensitizing the human subject. For example, it is easy to sensitize the guinea pig to egg white by repeated injections of the substance, but this technic fails to sensitize the human subject. Brunner,[11] working with a large group of atopic persons, failed to sensitize them (with possibly 1 exception) by repeated injections of such potent antigens as rabbit dander and egg. These results are different from those obtained in the lower animal with the same antigens.

There are, however, certain antigens which have the property of regularly stimulating reagin formation in the human subject. Such antibody formation will occur in nonatopic as well as in atopic persons. This artificially induced sensitivity is much more fleeting than sensitivity induced naturally. Rackemann and Stevens[12] demonstrated that extract of Ascaris is an excellent antigen for the production of reagins. Brun-

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7. Bell, S. D., and Eriksson, Z.: Studies in Transmission of Sensitization from Mother to Child in Human Beings: Transfer of Skin Sensitizing Antibodies, J. Immunol. **20**:447, 1931.

8. Walzer, M., in discussion on Bell, S. D.: Transfer of Skin-Sensitizing Antibodies, J. Allergy **2**:399, 1931.

9. Caulfeild, A. H. W.: The Correlation of Specific Sensitization as It Occurs Clinically in Man and as Induced Experimentally in Animals, Tr. Am. Climat. & Clin. A., 1937.

10. Coca, A.; Walzer, M., and Thommen, S.: Asthma and Hay Fever in Theory and Practice, Springfield, Ill., Charles C. Thomas, Publisher, 1931, p. 5.

11. Brunner, M.: Active Sensitization in Human Beings, J. Allergy **5**:257, 1934.

12. Rackemann, F. M., and Stevens, A. H.: Skin Tests to Extracts of Echinococcus and Ascaris, J. Immunol. **13**:389, 1929.

ner [11] confirmed this in his studies. Cooke and Spain [13] demonstrated the presence of skin-sensitizing reagins in nonatopic subjects after injections of horse serum. Tuft [14] showed that insulin as well as horse serum is capable of stimulating reagin formation.

The present work was undertaken to determine whether sensitivity to Ascaris lumbricoides, actively induced during pregnancy, could be transferred passively to the offspring. Subjects were selected from patients in the third trimester of pregnancy attending the prenatal clinic of the Beth Moses Hospital. The women chosen were nonatopic as far as could be ascertained. Preliminary intracutaneous tests with Ascaris extract (0.1 mg. of nitrogen per cubic centimeter) were performed. Only women giving a negative reaction were used for this study. After the initial test, weekly intracutaneous injections of 0.05 cc. of extract of Ascaris were given. Whenever possible these injections were continued until hypersensitiveness manifested by moderate or marked cutaneous reactions developed. The number of injections given varied from three to nine, the average being about five.

When the women were admitted to the hospital in labor, about 30 cc. of blood was taken from each. When the child was born blood was taken from the fetal cord. Studies of the serum of both the maternal and the fetal blood were then made by the Prausnitz-Küstner method. Tests with both serums were made on the same substitute, one arm being used for the maternal blood and the other for the fetal blood. At least two sites were prepared with each serum, and in the majority of cases two substitutes were used for each serum. One week was allowed to elapse between the time of cutaneous sensitization and that of testing.

In the accompanying table are presented data on 12 cases, including the dates of the intracutaneous injections, the reactions obtained with each after twenty minutes, the date of delivery when serum was obtained and the results of passive transfer tests with the maternal serum and the serum from the fetal cord.

In this series we were not able in every instance to induce moderate or marked reactions, because some patients failed to attend the clinic regularly and did not receive enough injections. In 9 cases in our series reagins for Ascaris were demonstrated readily. In 2 subjects who received four and seven injections respectively and who on their last visit to the clinic showed a 1 plus and a 3 plus reaction respectively, no skin-sensitizing antibodies could be demonstrated. In both cases three substitutes were used for the transfer tests, with consistently

13. Cooke, R. A., and Spain, W. C.: Studies in Hypersensitiveness, J. Immunol. **17**:295, 1929.

14. Tuft, L.: Insulin Hypersensitiveness: Immunologic Considerations and Case Reports, Am. J. M. Sc. **176**:707, 1928.

	Intracutaneous Injection of 0.05 Cc. of Ascaris Extract (0.1 Mg. Nitrogen per Cc.)			Number of Days Between Last Injection and Delivery	Results of Testing by Prausnitz-Küstner Method	
	Date of Sensitizing Injections	Reactions to Sensitizing Injections	Date of Delivery		Maternal Blood	Fetal Blood
B. S.	9/30/37	—	12/ 1/37	34	++++	—
	10/ 7/37	++				
	10/28/37	++				
M. F.	9/30/37	—	11/ 9/37	18	—	—
	10/ 7/37	+				
	10/14/37	+				
	10/21/37	++				
L. R.	10/ 2/37	—	11/16/37	10	++++	—
	10/16/37	—				
	10/19/37	—				
	10/30/37	+				
	11/ 6/37	++				
L. B.	10/ 2/37	—	1/ 2/38	23	—	—
	10/ 8/37	—				
	10/16/37	—				
	10/21/37	+				
	10/30/37	++++				
	11/20/37	++++				
	12/10/37	++++				
S. S.	10/ 7/37	—	12/27/37	11	++++	—
	10/14/37	—				
	10/21/37	—				
	11/ 4/37	+				
	11/11/37	—				
	11/18/37	+				
	12/ 1/37	+				
	12/16/37	++				
	12/19/37	+++				
V. M.	10/ 7/37	—	12/29/37	13	+++	—
	10/14/37	—				
	10/21/37	+				
	10/28/37	+				
	11/ 4/37	+				
	11/27/37	+				
	12/ 2/37	+				
	12/ 9/37	+				
	12/16/37	+++				
G. F.	11/ 6/37	—	3/ 1/38	17	+++	—
	11/11/37	—				
	12/ 4/37	+				
	12/11/37	+++				
	1/ 6/38	+++				
	2/ 3/38	+++				
	2/12/38	+++				
L. L.*	11/ 6/37	—				
	12/ 4/37	—				
	12/18/37	++				
	1/ 8/38	+++				
B. B.	11/ 6/37	—	3/ 3/38	29	++++	—
	12/ 8/37	++++				
	2/ 2/38	++++				
R. G.	12/ 2/37	—	3/18/38	22	+++	—
	12/ 9/37	+				
	12/30/37	++++				
	2/24/38	++++				
F. F.	12/ 2/37	—	4/25/38	81	+++	—
	12/ 9/37	—				
	12/16/37	+				
	12/27/37	+				
	2/ 3/38	+++				
C. C.	12/ 4/37	—	3/23/38	60	+++	—
	12/11/37	++				
	12/18/37	+++				
	12/30/37	++++				
	1/22/38	++++				

* No blood obtained.

negative results. In 1 of our cases blood was not obtained. *Reagins could not be demonstrated in serum from the fetal cord in a single instance.*

COMMENT

It is now generally agreed that guinea pigs can be sensitized to most of the common antigens and that such sensitivity can be transmitted passively through the placenta to the offspring, in a certain percentage of cases to the third generation. It is further recognized that many of the human antibodies, such as the antitoxins, are transmitted through the placenta to the fetus. There is no experimental evidence, however, to show that antibodies responsible for human hypersensitiveness can be transmitted through the placenta.

Up to the present, all experimental work on the placental transmission of human hypersensitiveness has dealt with natural sensitivity. In the present work we have chosen nonatopic subjects and have actively induced sensitivity in them. With this technic the offspring might become sensitive in two ways: First, they might become actively sensitized by the passage of antigen through the placenta. There are 2 cases in our series (table) in which eighty-one and sixty days, respectively, elapsed between the time of the last injection and the time of delivery, periods sufficient to permit active sensitization to take place. This did not occur. Second, the offspring could have become passively sensitized by the passage through the placenta of reagins in the maternal blood. We failed to demonstrate reagins in the fetal blood in any case. This suggests that sensitization of the pregnant woman does not affect the fetus. It offers evidence which refutes the theory that intrauterine sensitization of the human fetus is easily accomplished.

SUMMARY

Twelve nonsensitive pregnant women were given intracutaneous injections of Ascaris extract at weekly intervals.

At the termination of pregnancy blood was drawn from the mother and from the fetal cord.

The maternal serum and serum from the cord were tested by the Prausnitz-Küstner method for the presence of reagins for Ascaris.

Reagins for Ascaris were demonstrated in 9 of the 11 specimens of maternal blood.

Reagins were absent in the corresponding 11 specimens of fetal blood.

Case Reports

MULTIPLE CYSTIC TUBERCULOSIS OF BONE IN A CHILD

FURTHER OBSERVATIONS ON A CASE; ROENTGEN PROGRESS FOR TWO YEARS

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The present communication concerns the case of multiple cystic tuberculosis of the bones which I reported in a previous issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN.[1]

Multiple cystic tuberculosis involving the small long bones of the hands or feet or the long hollow bones is rare in adults or children. The earlier reports indicated that this condition affects only young adults and that the lesions are characteristically confined to the small bones of the hands and feet. Emphasis was placed on distinct types of lesions visible on roentgen observation. Jüngling [2] described two main types, the diffuse and the circumscribed. In the diffuse type both the cortex and the medulla of the bone are involved with a weblike structure of increased density. The diameter of the bone is increased, and destruction of a phalanx may occur. Sclerosis is negligible. The circumscribed type consists mainly of a punched-out area of decreased density, with a thin cortex and no surrounding sclerotic reaction. This type represents a healing or cystic stage and is characterized by its chronicity.

In the last ten years 11 cases of this rare form of tuberculous disease of the bone in children have been recorded in the literature, which shows that the disease occurs in children as well as in adults.[1] These cases and those of adults reveal that the lesions may attack the long hollow bones or the long small bones of the hands and feet and that there may be different degrees of osseous involvement which are merely stages of a tuberculous process and not distinct types of the disease.[3]

From the Department of Pediatrics and Infectious Diseases, the Medical School, University of Michigan.

1. Law, J. L., and Perham, W. S.: Multiple Cystic Tuberculosis of the Bones in Children, Am. J. Dis. Child. **56**:831 (Oct.) 1938.

2. Jüngling, O.: Fortschr. a. d. Geb. d. Röntgenstrahlen **27**:375, 1920; Beitr. z. klin. Chir. **143**:401, 1928.

3. Petter, C. K., and Mendelman, J. P.: Am. Rev. Tuberc. **32**:285, 1935. Sanes, S., and Smith, W. S.: Osteitis Tuberculosa Multiplex Cystica of the Fibula and Tibia, J. A. M. A. **102**:1206 (April 14) 1934. Von Alstyne, G. S., and Gowen, G. H.: J. Bone & Joint Surg. **15**:193, 1933.

REPORT OF A CASE

On March 25, 1935, a 6 year old girl was admitted to the pediatric service of the University Hospital with the complaint that she had been in failing health for nine months, with loss of appetite, loss of weight, ease of fatigue and some night sweats; for four months there had been a deformity of the back. This had been treated by her physician for three months with a body cast. The family history, past history and history of contact with tuberculosis were negative. All ingested milk had been pasteurized. A detailed history was given in the first report.

Physical examination on the child's admission showed that she was well developed and fairly well nourished, 44½ inches (113 cm.) tall and weighing 37¼ pounds (16.9 Kg.). The general physical examination gave negative findings except for kyphosis in the midthoracic region, with protuberance of three vertebrae and some tenderness to pressure. The reaction to an intracutaneous tuberculin test with a dilution of 1:1,000 was 2 plus. A roentgenogram of the spine and chest showed a destructive process involving the bodies of the seventh, eighth and ninth thoracic vertebrae and gross tuberculous peritracheal and peribronchial adenopathy with no parenchymal lesion.

Incidental to the first roentgen examination a destructive lesion was noted in the left humerus, and with additional study of the bones lesions were observed in both scapulas, both clavicles, the skull, the left humerus and radius, the right humerus and radius, the first, fourth, fifth, sixth and ninth ribs on the left, the left iliac bone, the third and fifth lumbar vertebrae, the right and left tibia and the left fibula. The lesions were characterized by circumscribed areas of rarefaction with little or no surrounding sclerosing reaction.

The cytologic and chemical study of the blood gave negative results. The urine contained no Bence-Jones protein. Microscopic study of material from the right scapula showed active chronic tuberculous osteomyelitis and perichondritis. Because of these observations the far-flung destructive osseous lesions were considered to be tuberculous.

For twenty-eight months the patient was under close supervision at home or in the University Hospital. For treatment a Bradford frame and general supportive dietetic and hygienic measures were used. Periodic roentgen examinations of the various osseous lesions showed the progress of the disease. Because of advance in the tuberculous spinal process a spinal fusion, with the Hibbs technic, was performed in December 1935.

The general condition of the patient improved, as shown by a 14 pound (6.4 Kg.) gain in weight and an essentially afebrile course, until June 1937. Then the girl had daily elevations of temperature to 101.5 F. In July she was sent to the Michigan State Tuberculosis Sanatorium for further care.

In October a swelling appeared in the right axilla; this broke down and discharged purulent material revealing a sinus tract which led to a small group of moderately enlarged lymph nodes. The swelling had subsided by December. The daily elevations of temperature gradually subsided, and during April and May 1938 the child was afebrile. While at the sanatorium she has continued to gain in weight; in May 1938 she weighed 63 pounds (28.6 Kg.) (normal weight, 55 pounds [24.9 Kg.]), as compared with 37 pounds (16.8 Kg.) at the beginning of treatment, in March 1935. At the time of writing the general physical condition is excellent.

Roentgenograms made in January 1938 showed no visible evidence of disease of the bones except in the right shoulder and the spine. The scapula and the head of the humerus showed some destruction. No remains of the previous spinal fusion could be seen. In May the right shoulder showed marked improvement, with increased calcification and some restoration of the head of the humerus. The spine showed satisfactory bony fusion, with healing of the anterior vertebral bodies. The patient is asymptomatic and is to begin mild activity.

SUMMARY

Further observations on a rare case of cystic tuberculosis of many bones in an 8 year old child are recorded. Roentgen study of the course of these lesions during a two year period is reported. It is briefly pointed out that this disease occurs in both the adult and the child and that so-called types are merely stages in a chronic tuberculous process.

CHONDRODYSPLASIA: HEREDITARY MULTIPLE CARTILAGINOUS EXOSTOSES

REPORT OF FIVE CASES IN A NEGRO FAMILY

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Chondrodysplasia is a comparatively uncommon hereditary osseous dystrophy which usually becomes manifest in infancy or in early childhood. It is characterized by expansion of the ends of the long bones and by multiple cartilaginous and osteocartilaginous growths within and on the skeletal system. These result from a disturbance in growth which affects the proliferation and the ossification of the bone-forming cartilage. The condition is a distinct clinical entity not to be confused with the occasional traumatic or mechanical exostosis found near the epiphysial end of a long bone.

The first case in this country was reported by Gibney [1] in 1875; however, the condition received little recognition in America prior to Ehrenfried's [2] papers in 1915 and 1917. Stocks [3] in 1925 brought the number of total cases reported in the world literature up to 765.

The disease is protean in character: It may manifest itself simply as small cartilaginous exostoses which cause the patient no concern, or there may be great deformity and distortion of the skeletal system with considerable functional disability. Ollier [4] has described a form of the disorder with unilateral distribution of the lesions. Blount [5] reported a case in which exostoses were absent.

This variability probably accounts for the multiplicity of names which have been used to designate this clinical entity. The more common are chondrodysplasia, dyschondroplasia, hereditary multiple cartilaginous

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1. Gibney, V. P.: Multiple Exostoses, M. Rec. **10**:300, 1875.

2. Ehrenfried, A.: (*a*) Multiple Cartilaginous Exostoses, J. A. M. A. **64**: 1642 (May 15) 1915; (*b*) Hereditary Deforming Chondrodysplasia, ibid. **68**:502 (Feb. 17) 1917.

3. Stocks, P.: Hereditary Disorders of Bone Development, London, Cambridge University Press, 1925.

4. Ollier, M.: De la dyschondroplasie, Bull. Soc. de chir. de Lyon **3**:22, 1899; cited by Mahorner, H. R.: Dyschondroplasia, J. Pediat. **10**:1 (Jan.) 1937.

5. Blount, W. P.: Chondrodysplasia: An Unusual Case, Am. J. Dis. Child. **40**:327 (Aug.) 1930.

exostoses, Ollier's disease, diaphysial aclasis (Keith), multiple congenital osteochondromas and hereditary deforming chondrodysplasia.

The disease in all probability results from a congenital developmental anomaly which affects primarily the osseous system. According to Davis [6] and Honeij,[7] in some cases the condition has been recognized at birth. Dwyer [8] reported a case in a 20 month old infant, and Lewin [9] recorded a case in which exostoses were noted at the age of 5 months. However, the disorder is usually first noticed in late infancy or early childhood, the characteristics becoming more obvious with skeletal maturity.

Concerning the cause, Hyndman [10] stated:

> Although the primary factor is not established, it would seem . . . that cartilage rests are left in the wake of a chaotic advancing epiphysis, and these rests undoubtedly form the nucleus of the anomalous benign tumors . . . whether one encounters a sessile tumor on the shaft or a central tumor expanding the cortex depends on the location of the cartilage rest.

Even after skeletal maturity is reached, these irregular clumps or nests of cartilage cells persist, partly uncalcified and scattered throughout the metaphysis, giving to the bone a cystic appearance on roentgen examination. Incidentally, they may later develop into cartilaginous exostoses, or chondromas. The microscopic picture is not unlike that of chondroma.

According to Ray,[11] the most tenable theory and the one generally accepted is that there is inheritance of a faulty anlage for the tissue producing the intermediary cartilage, on the one hand, accompanied by what Keith [12] termed a growth disturbance in the modeling or pruning of the diaphysis (diaphysial aclasis), on the other hand.

Although chondrodysplasia has been described as affecting practically every racial group, the American literature is particularly scanty in cases

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6. Davis, G. G.: Multiple Cancellous Exostoses, Am. J. Orthop. Surg. **3**:234, 1905-1906.

7. Honeij, J. A.: A Study of Multiple Cartilaginous Exostoses, Arch. Int. Med. **25**:584 (June) 1920.

8. Dwyer, H. L.: Multiple Cartilaginous Exostoses, Am. J. Dis. Child. **19**: 189 (March) 1920.

9. Lewin, P.: Multiple Cartilaginous Exostoses, Surg., Gynec. & Obst. **45**: 48 (July) 1927.

10. Hyndman, O. R.: Hereditary Deforming Chondrodysplasia, Arch. Surg. **21**:12 (July) 1930.

11. Ray, H. H.: Diaphysial Aclasis, Arch. Pediat. **47**:152 (March) 1930.

12. Keith, A.: Studies on the Anatomical Changes Which Accompany Certain Growth Disorders of the Human Body: I. The Nature of the Structural Alterations in the Disorder Known as Multiple Exostoses, J. Anat. **54**:101, 1919-1920.

involving the Negro race. Hale,[13] in discussing the racial aspect of the disease, stated: "Few Negroes are affected in America, Anglo-Americans predominate." Lewin[9] said: "The condition is rare in the colored race."

Ehrenfried,[2] who reviewed the American literature in 1917, was able to find only 1 case in a Negro in a total of 99 collected cases. This case was reported by Ashhurst.[14] In 1930 Ray[11] published a review of 58 additional cases, which appeared in the American literature subsequent to Ehrenfried's report. His collection included a single case in a Negro, reported by Lewin.[9] More recently Mahorner[15] reported a third case involving this racial group. These 3 cases of chondrodysplasia in the Negro are the only ones I have been able to find among the 160 or more cases which have appeared to date in the American medical literature.

Incidentally, the well known hereditary feature, present in 83 per cent of the cases reviewed by Ehrenfried, was absent in all 3 cases. Ashhurst's patient, an 11 year old girl, exhibited several exostoses; however, no one else in her family had any similar affliction. Moreover, in Mahorner's case, that of an 18 year old Negro boy with multiple bony prominences, there was no family history of a similar condition. Lewin's case, that of a 14 year old Negro girl, is included here with reservations because it was designated by the author as probably a case of true hypertrophic chondrodystrophy, a disease held by some to be quite unlike the bony dystrophy discussed in this paper. Lewin's report included no roentgenograms, and again no mention was made of a familial tendency.

Because of the rarity of reported cases of chondrodysplasia in the Negro race and because of the total absence of the hereditary feature in those reported to date, the following cases, which involved 5 members of a Negro family, are submitted.

Two girls of this family, aged 8 and 11 years, respectively, were recently examined in the pediatric clinic of the Provident Hospital. In both numerous small bony prominences were discovered on various parts of the skeletal system. The true nature of these abnormal growths having been suspected, other members of the immediate family were investigated, and similar growths were found in the father and in 2 of the other children. Of the siblings examined, only 1 was found to be free from the disease. The mother and 1 child were not available for examination.

13. Hale, K.: Hereditary Deforming Chondrodysplasia or Multiple Exostoses, Ann. Surg. **92**:92 (July) 1930.

14. Ashhurst, A. P. C.: Multiple Cartilaginous Exostoses (Hereditary Deforming Chondrodysplasia), Ann. Surg. **63**:167 (Feb. 16) 1916.

15. Mahorner, H. R.: Dyschondroplasia, J. Pediat. **10**:1 (Jan.) 1937.

REPORT OF CASES

CASE 1.—D. R., a Negro girl aged 8 years, was referred to the clinic because of enuresis. She was born at term of a normal labor and weighed 12 pounds (5,443.2 Gm.) at birth. Palpation revealed hard irregular bony excrescences in the regions of the knees, ankles, clavicles, wrists, costochondral junctions, vertebral borders of the scapulas and proximal ends of the arms.

Roentgen study of the left humerus revealed that the proximal third of the bone was irregular, expanded and cystic. The cortex was thinned, and several small exostoses were present. The center of the metaphysis was occupied by several punched-out osteoporotic areas suggestive of enchondromas.

Exostoses were also visualized near the distal extremities of the left ulna and the fifth metacarpus as well as in the region of the malleoli, ribs, clavicles and dorsum of each scapula.

Roentgen study of the knees showed broad irregular tibial and femoral metaphyses deformed by exostoses, punched-out cystic areas and longitudinal striations. The fibular heads were osteoporotic and irregular in outline, with extremely thin cortices.

CASE 2.—R. R., a Negro girl aged 11 years, a sister of D. R., was born at term of a normal labor and weighed 10 pounds (4,536 Gm.) at birth. For the six years before examination she had been 5 to 8 pounds (2.3 to 3.6 Kg.) underweight for her age and height; however, she had never been seriously ill.

Examination revealed a fairly well developed but poorly nourished child 52½ inches (131.3 cm.) tall, weighing 59 pounds (26.8 Kg.). Hard irregular projections, painless and attached to bone, were palpated in the region of the knees, ankles, clavicles, scapulas, iliac crests, costochondral junctions, proximal ends of the arms and anterior iliac processes. The middle finger of each hand was of somewhat increased length, and the right one exhibited a fusiform enlargement at the junction of the proximal and the middle phalanx.

A representative roentgenogram of the right forearm showed that the metaphysis of the radius was wide for an abnormal distance up the shaft and was imperfectly ossified. The cortex of the radius was thinned, and the bone was deformed by several exostoses.

Bullous juxtaepiphysial enlargements appeared at the proximal ends of the phalanges, this phenomenon being most prominent in the middle phalanx of the right middle finger.

The femoral and tibial metaphyses of the knees were widened and of abnormal length. Defective calcification was denoted by soap bubble areas of osteoporosis. Exostoses were present on the metaphyses of all four of these bones as well as on the proximal ends of the fibulas, which were fused with the tibias.

A punched-out cystic area occupied the center of the right distal tibial metaphysis.

CASE 3.—R. R., a brother of the other children, was brought to the clinic at the age of 4 years for a routine examination. He was born prematurely at the end of a seven month gestation, weighing 4 pounds (1,814.4 Gm.). He was breast fed for the first three months. The first tooth appeared at the age of 10 months, and the child walked at 2 years.

Examination revealed a poorly developed and poorly nourished boy who appeared small for his age. The weight was 22¾ pounds (10.3 Kg.) and the height 33½ inches (83.8 cm.). Sharp abnormal bony prominences were palpated

on the ribs and left arm. Roentgen study showed these masses to be typical exostoses. In 1936 the patient died in another hospital.

CASE 4.—A. R. (fig. 1), a 6 year old sister of the other children, was brought to the clinic for examination on request because multiple exostoses had been discovered in other members of the family.

She was born at term of a normal labor, weighing 7 pounds (3,175 Gm.). She was breast fed. Her development was regarded as normal except that she had always been underweight.

Fig. 1 (case 4).—A. R. at the age of 6 years and weighing 30 pounds (13.6 Kg.). Note the beading of the ribs, dwarfing, genu valgum and exostoses on the dorsum of each scapula. Such a picture might be confused with that of rickets.

She appeared poorly developed, poorly nourished and obviously dwarfed for her age, the height being 38½ inches (96.3 cm.), the weight 30 pounds (13.6 Kg.) and the occipitofrontal circumference of the head 19 inches (48 cm.).

Examination of the skeletal system disclosed hard irregular painless prominences in the region of the knees, wrists, ankles, vertebral borders of the scapulas, ends of the clavicles and proximal extremities of the arms. There was a double row of rosary-like nodules on the ribs, one row occupying the midclavicular line and the other the anterior axillary line. A genu valgum deformity was present (fig. 1).

The roentgenogram of the chest and arms showed exostoses on the fifth, sixth and seventh ribs in the right midclavicular line. The proximal thirds of the humeri were somewhat expanded and irregularly ossified.

The bones of the pelvis were thickened and irregular, this deformity being most pronounced along the iliac crest and the acetabular roof on the left, where small exostoses appeared. The proximal ends of the femurs were somewhat club shaped, which resulted in partial obliteration of the normal angle between the neck and the shaft. The metaphysis of the left femur had a thinned cortex, and the soap bubble areas indicated imperfect calcification.

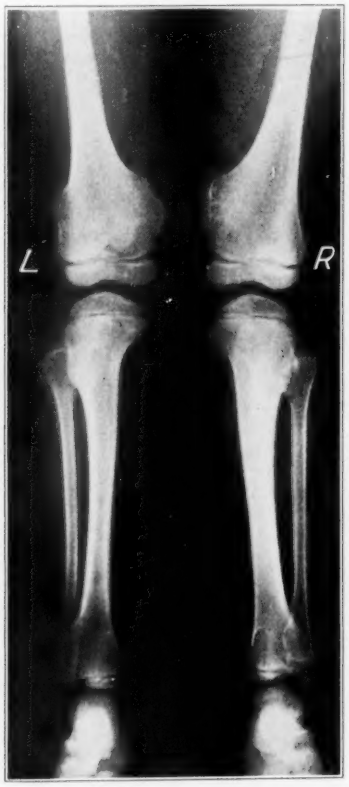

Fig. 2 (case 4).—The metaphyses are distorted by the exostoses, defective ossification and thinned cortices. The exostoses and the increased width of the metaphyses largely account for the genu valgum deformity. The knees form a favorite location for exostoses in patients with this bony dystrophy.

The roentgenogram of the knees (fig. 2) showed exostoses, punched-out cystic areas, thinned cortices and irregular ossification involving the metaphyses, the abnormal length and width of which produced the genu valgum deformity. Similar lesions were visualized in the bones of the ankles.

CASE 5.—E. R., a Negro 38 years old, father of the children, stated that hard painless bony projections had been present in the region of his knees all of his

life. He also stated that his father, his brother and his brother's son were similarly affected; however, his sister was spared (fig. 3). His past medical history was irrelevant.

He appeared well nourished and muscular; however, he was short, squat and definitely dwarfed, and lordotic and slight genu valgum deformities were present. He weighed 120 pounds (54.5 Kg.); his height was 58½ inches (146.2 cm.); the circumference of his head was 25 inches (55 cm.), and the center of his body fell at a point several centimeters above the pubic symphysis.

The dwarfed stature, lordosis, short arms and trident right hand were somewhat suggestive of achondroplasia.

Palpation revealed prominent painless bony masses over which the skin was freely movable in the region of the ankles, knees, iliosacral synchondroses and arms and on the seventh and eighth ribs on the right, at their costochondral junctions.

Just below the right hip joint one could easily palpate a hard painless irregular bony mass projecting apparently from the anteromedial aspect of the proximal end of

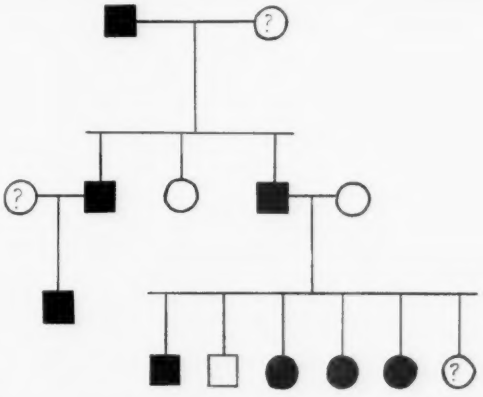

Fig. 3.—Family tree showing the incidence of hereditary chondrodysplasia in a Negro family. A square indicates male; a circle, female; a black square or circle, exostoses, and a question mark, status with regard to exostoses not known. The ratio of affected males to affected females is 5:3.

the femur. This mass was visibly prominent and interfered slightly with adduction of the thigh. The right lower extremity was 2.5 cm. shorter than its fellow.

Roentgen study of the pelvis (fig. 4) showed a large osteochondroma of cauliflower-like appearance attached to the medial aspect of the right femur at the level of the lesser trochanter. It was of unequal density and was circular, with a diameter of approximately 3 inches (8 cm.). The right acetabulum appeared extremely large and flattened. There was a small ovoid area of varying degrees of calcification in the region of the right posterior superior iliac spine.

Both femoral necks appeared shortened, stubby and thickened. The metaphysial regions were vacuolated and poorly calcified. The proximal third of the left femur presented exostoses on both medial and lateral aspects.

Roentgen examination of the knees (fig. 5) showed that the metaphysis of the right femur extended too far up the shaft, giving the distal end of this bone a square shape. There was a prominent pedunculated spur at the junction of the metaphysis and the shaft on the medial aspect. The level of the right knee

Fig. 4 (case 5).—A large cauliflower-like osteochondroma distorts the neck and the metaphysis of the right femur. The right acetabulum is large and shallow. Several exostoses appear on the left femur in the region of the trochanters.

Fig. 5 (case 5).—The metaphyses are unusually long and broad, particularly at the distal end of the right femur, where a prominent osteocartilaginous exostosis appears. The fibular metaphyses are irregular and expanded and have fused with the tibias. The level of the right knee joint is 2.5 cm. above that of the left.

joint was about 2.5 cm. above that of the left. Longitudinal striations and stippling were present in all of the bones at the knees. The heads of the fibulas, which had fused with the tibias, appeared somewhat expanded and cystic, with extremely thin cortices.

LABORATORY DATA

The Wassermann and the Kahn reaction of the blood were negative in all of the cases. Determinations of blood calcium and phosphorus yielded no significant deviation from normal values in any instance. Mild secondary hypochromic anemia was present in 2 of the cases (2 and 4). Urinalyses yielded normal findings. Roentgenograms of the skull showed neither exostoses nor any other abnormality. There was no evidence of mental retardation in any of the cases.

COMMENT

These cases illustrate the usual familial character of this disease, which shows a tendency to conform to the mendelian law of inheritance, occurring predominantly in males, in the ratio of 3:1. The family tree of the Negroes described here shows a male predominance of 5:3 in the affected members. The line of descent appears to be definitely more paternal than maternal.

Characteristically, the sites of predilection for the skeletal anomalies in these cases were the metaphyses of the long bones, the costochondral junctions, the cristal borders of the pelves, the scapulas and the clavicles. The membranous bones of the face and skull were not involved.

Multiple exostoses involving various parts of the skeleton were present in each case. They are said to have a special predilection for the region of the knees, where their almost invariable presence may result in a genu valgum deformity, as in cases 2, 4 and 5.

More or less dwarfing of stature, seen in each of the cases except the first, is characteristic of the disease, and it becomes more obvious as skeletal maturity is reached. The lack of growth affects the lower extremities, not the trunk, and is due to premature union of the epiphysis with the shaft.

Of interest is the fact that enlargements at the costochondral junctions (rosary) occurred in all of the cases. Exostoses in this location, while possibly lacking the smooth, rounded contour of the typical rachitic rosary, on superficial examination may nevertheless be confused with the true rachitic rosary in a Negro child who also presents dwarfing of stature and genu valgum deformity, as in case 4. Apparently such gross findings as beading of the ribs, knock knees and dwarfing may occur in cases of hereditary multiple exostoses uncomplicated by rickets.

Roentgenograms in these cases revealed the following characteristic features: (1) excessive length and width of the metaphyses due to incomplete conversion of the metaphysis into the diaphysis; (2) irregular and incomplete ossification of cartilage rests, indicated by cystic and

osteoporotic areas, and (3) multiple exostoses, which formed a prominent but not fundamental finding.

The diagnosis of chondrodysplasia is usually made without difficulty. In isolated cases, however, other conditions must occasionally be excluded. Roentgenograms of the enchondromas in cases of this skeletal dystrophy often present soap bubble vacuolations which may roughly simulate such cystic bone diseases as benign bone cyst, giant cell tumor and Recklinghausen's osteitis fibrosa cystica. The infrequent resemblance to rickets has already been mentioned. However, in each instance the history together with physical, blood chemical and roentgen findings usually indicates the true diagnosis, which makes biopsy rarely necessary.

Some of the findings presented by the father of the children (dwarfism, beading of the ribs, bony swellings about the epiphysial ends of the long bones, lordosis and trident hand) also commonly appear in cases of chondrodystrophia foetalis. On this basis some authors [16] have stressed a possible relation between this disease and hereditary multiple exostoses. Other writers [17] have expressed the opposing view, that there is no relation between the two bony dystrophies.

Chondrodysplasia commonly remains symptomless throughout the life of the victim, who often is ignorant of its presence. Malignant degeneration occurred in about 5 per cent of Ehrenfried's collected cases. The pressure on nerves, vessels or viscera from exostoses is practically the only indication for treatment.

SUMMARY

Five cases of chondrodysplasia in a single Negro family are reported, making a total of 8 cases involving the Negro race recorded to date in the American literature.

The characteristic hereditary feature of the disease was apparently absent in the 3 cases in Negroes previously reported by other authors.

Dr. B. W. Anthony interpreted the roentgenograms.

426 East Fifty-First Street.

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16. Dwyer.[8] Lewin.[9] White, J. R.: Two Rare Bone Diseases: Hereditary Deforming Chondrodysplasia and Chondrodystrophia Foetalis, Brit. J. Surg. **12**: 76 (July) 1924.

17. Hyndman.[10] Ray.[11] Carman, R. D., and Fisher, A. O.: Multiple Congenital Osteochondromata, Ann. Surg. **61**:142, 1915.

KALA-AZAR

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Kala-azar is distinctly a rare disease in the United States; only 4 cases of this infection in children have been reported in the American literature. The first of these was described by Talbot and Lyon [1] in 1918, the second by Faber and Schussler [2] in 1923 and the third by Wollstein [3] in 1925. In 1934 Ginandes [4] presented an excellent review of the literature and included the report of a case observed by him. The case to be reported here constitutes the fifth on record and the second to be studied in the Babies Hospital, that of Wollstein having been the first.

All of the patients were born in countries where kala-azar is known to be endemic. Two were born in Greece, 1 in Italy and 1 in Sicily. The subject of the present report was born in Sicily. All cases have been reported from seaport towns in the United States.

REPORT OF A CASE

Yole G., aged 13 months, a white child of Italian extraction, was admitted to the Babies Hospital on Sept. 27, 1934, with complaint of irregular fever and pallor.

The father and mother and two siblings were in good health. There was no family history of tuberculosis or syphilis; no illness similar to that of the patient had been noted in other members of the family.

The child was born in Furci Sicolo, province of Messina, Sicily. Her delivery, which occurred at full term, was normal and spontaneous; it was performed by a midwife; the weight at birth was not recorded. The neonatal period was uneventful, there being no cyanosis, convulsions, jaundice or hemorrhagic manifestations. The child had been breast fed until one week before admission; subsequently she had received undiluted cow's milk. Neither cod liver oil nor orange juice had been administered.

From the Department of Diseases of Children, College of Physicians and Surgeons, Columbia University, and the Babies Hospital.

1. Talbot, F., and Lyon, A. B.: Kala-Azar in a Child, Am. J. Dis. Child. **16**:154 (Sept.) 1918.

2. Faber, H. K., and Schussler, H.: Leishmaniasis in the United States, J. A. M. A. **80**:93 (Jan. 13) 1923.

3. Wollstein, M.: A Case of Kala-Azar in an Infant, New York State J. Med. **25**:413, 1925.

4. Ginandes, G. J.: Kala-Azar in Children, Am. J. Dis. Child. **48**:1336 (Dec.) 1934.

The onset of the present illness was insidious. The child was said to have been in good health and developing normally until two or three months before admission to the hospital. At about this time increasing pallor was noted, and an irregular, spiking fever made its appearance. The patient became weak and listless and lost interest in her previous activities. The appetite was fairly good until two weeks before admission; subsequently marked anorexia was noted. The child had vomited only once, about a week before admission; the vomitus was not unusual. Bowel movements had been normal, with an increasing tendency to constipation; there was no history of melena or hematuria. The child had been free of cough and infection of the upper part of the respiratory tract. The exact weight was never known, but it was thought she had lost from 3 to 5 pounds (1,307 to 2,268 Gm.) since the onset of illness. There was exacerbation of all symptoms during the two weeks previous to admission.

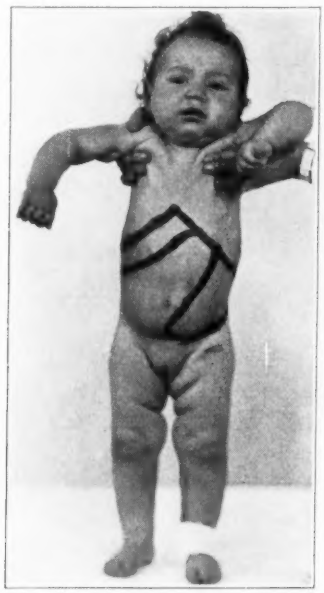

Fig. 1.—Photograph of the patient taken on her admission to the hospital.

Physical examination on admission revealed that the child was well developed and fairly well nourished; the temperature was 100 F. The patient appeared chronically ill and when disturbed responded in a tired manner. There were pallor and slight icterus of the skin and mucous membranes. The head showed slight parietal bossing; both fontanels were closed; the circumference was 44 cm. Examination of the eyes, including the fundi, revealed nothing abnormal except an icteric tint of the scleras. The tympanic membranes were normal. The mucous membranes of the nose and throat gave evidence of severe anemia; the gums and teeth were in good condition. The heart was not enlarged; the rate and rhythm were normal; over the mitral area there was a soft systolic murmur which was not transmitted. The blood pressure was 64 mm. of mercury systolic and 40 mm. diastolic. The lungs were clear to percussion and on ascultation; no rales were heard. The abdomen was protuberant. The spleen was tremendously enlarged.

extending to the midline and filling the entire left side of the abdomen. The liver was also enlarged, extending 7 cm. below the costal margin in the midclavicular line. Both organs presented a smooth, firm, nontender surface. The kidneys

TABLE 1.—*Hematologic Determinations During the Course of the Disease*

Date	Hemoglobin		Red Blood Cells, Million	Platelets	White Blood Cells	Differential Count, Percentage					Schilling Count	Reticulocytes, Percentage
	Gm.	Percentage				Polymorphonuclears	Eosinophils	Lymphocytes	Monocytes	Myelocytes		
10/27/34	4.8	28	1.8	.....	3,820	21	..	79	..	..	.....	....
10/29/34	4.4	26	2.2	76,000	4,800	24	..	70	4	1	4-20-0	4.80
10/30/34	4.4	26	2.0	64,000	6,150	21	..	71	..	2	.....	2.90
10/31/34	4.4	26	1.8	70,000	4,500	17	..	72	5	6	3-14-10	2.80
11/ 2/34	5.9	35	2.5	46,000	4,750	26	..	76	6	1	.....	....
11/ 3/34	7.3	43	3.0	60,000	2,250	25	..	72	..	..	.....	1.80
11/ 5/34	5.4	32	2.4	56,000	2,750	46	..	49	..	5	.....	1.00
11/ 6/34	7.6	45	3.2	54,000	3,550	38	..	57	3	2	13-24-1	1.20
11/ 8/34	9.0	53	3.1	64,000	4,400	36	..	55	5	3	6-28-22	....
11/ 9/34	9.8	58	3.6	78,000	3,250	22	..	74	2	1	2-19-21	0.45
11/12/34	8.8	52	3.3	70,000	3,050	29	..	69	..	1	0-28-1	1.30
11/13/34	8.0	41	2.5	76,000	2,900	15	..	80	3	..	1-13-1	....
11/15/34	9.8	58	3.1	64,000	4,500	27	..	67	6	..	3-22-2	0.36
11/16/34	10.7	63	3.4	120,000	3,950	39	..	57	4	..	3-32-4	0.36
11/18/34	10.5	62	3.4	106,000	6,000	36	..	53	11	..	.....	0.48
11/19/34	9.8	58	2.8	106,000	5,200	28	..	68	4	..	6-21-1	1.10
11/20/34	9.0	53	2.9	.....	6,450	30	..	69	1	..	3-26-3	3.40
11/22/34	9.0	53	3.0	102,000	4,400	28	..	63	5	3	2-24-2	8.10
11/23/34	8.5	50	2.5	82,000	3,800	39	..	59	2	..	5-31-3	....
11/24/34	8.5	50	2.5	92,000	3,950	32	..	55	10	3	0-31-1	....
11/26/34	7.6	45	2.4	86,000	5,200	31	..	67	..	2	4-22-5	4.20
11/28/34	8.5	50	2.8	118,000	5,000	35	..	65	..	..	9-24-2	4.00
11/30/34	10.7	63	3.1	134,000	3,850	27	..	71	2	..	7-17-3	3.60
12/ 3/34	11.7	69	3.5	.....	5,450	23	..	77	..	..	2-20-1	1.90
12/ 6/34	12.5	74	3.8	160,000	4,500	25	..	66	8	..	.....	1.30
12/10/34	12.7	76	3.7	128,000	6,450	28	..	65	7	..	7-14-7	0.92
12/13/34	12.5	74	3.6	200,000	6,450	39	..	60	1	..	2-27-10	2.20
12/17/34	11.5	68	3.6	106,000	6,550	37	..	52	10	1	2-28-7	....
12/20/34	9.0	53	2.9	264,000	5,500	43	..	44	12	1	3-31-9	5.80
12/22/34	7.1	42	2.3	392,000	5,560	42	..	53	1	4	2-27-3	6.40
12/24/34	8.6	51	2.8	336,000	4,800	54	..	37	6	3	1-40-13	....
12/26/34	6.2	37	2.2	392,000	4,750	53	..	37	10	..	4-39-10	....
12/28/34	8.1	48	2.9	352,000	5,800	53	..	44	3	..	2-35-11	11.00
12/31/34	8.5	50	3.0	392,000	4,200	48	..	47	5	..	1-35-12	10.70
1/ 3/35	6.6	39	2.2	384,000	5,150	44	..	49	6	2	0-37-7	11.80
1/ 7/35	7.3	43	2.3	160,000	5,050	43	..	53	..	2	5-30-10	10.80
1/10/35	11.6	69	3.7	90,000	4,500	54	..	44	1	1	.....	12.50
1/11/35	11.3	67	3.3	58,000	4,450	69	..	28	..	2	2-58-9	12.20
1/12/35	10.2	60	2.9	68,000	3,800	57	1	42	..	..	2-50-5	13.50
1/14/35	13.2	78	3.7	86,000	2,900	52	..	41	3	3	4-41-7	....
1/15/35	13.6	80	3.9	104,000	4,500	31	..	65	3	1	1-25-5	....
1/16/35	13.0	77	3.5	90,000	2,250	57	..	41	2	..	9-36-12	3.80
1/17/35	13.2	78	3.5	120,000	6,550	57	..	41	1	1	1-46-10	4.30
1/18/35												
a.m.	11.9	70	3.1	104,000	6,050	56	..	35	7	2	5-46-5	4.10
p.m.					4,400	54	..	39	4	3	7-36-11	....
1/19/35	11.5	68	2.8	128,000	4,300	55	..	40	2	2	2-47-6	4.10
1/21/35												
a.m.	11.9	70	3.2	144,000	3,600	64	1	25	5	2	2-55-7	3.00
p.m.					4,358	58	..	36	4	..	1-43-14	....
1/23/35	12.0	71	3.4	192,000	5,550	53	..	47	..	..	6-38-9	1.00
1/24/35	12.0	71	3.3	160,000	5,950	56	2	26	13	2	0-39-17	0.90
1/25/35												
a.m.	11.9	70	3.3	384,000	5,350	63	..	34	2	..	2-54-7	1.20
p.m.	11.9	70	3.4	248,000	5,000	40	..	59	..	..	3-32-5	1.00
1/28/35	11.0	65	3.0	208,000	8,950	64	..	33	2	..	1-41-22	1.60
1/29/35	11.7	69	3.3	320,000	7,950	73	..	15	10	2	1-65-7	3.40
1/31/35	11.2	66	3.1	128,000	7,150	58	..	36	1	4	5-52-1	2.80
2/ 2/35	8.1	48	2.3	104,000	6,450	73	..	21	6	..	5-28-10	....

were not palpable. At no site was there tenderness or rigidity. There was no conspicuous enlargement of the lymph nodes. The extremities were normal; there was no edema. Examination of the central nervous system disclosed no

abnormalities. The skin was not abnormal except for the pallor and slight jaundice. The child weighed 9,900 Gm.

Examination of the blood taken on admission showed: 4.8 Gm. of hemoglobin per hundred cubic centimeters (28 per cent Sahli); there were 1,800,000 erythrocytes and 3,820 leukocytes per cubic millimeter; of the latter, 21 per cent were polymorphonuclears and 79 per cent lymphocytes; a stained smear disclosed anisocytosis, poikilocytosis, achromasia, polychromatophilia and occasional normoblasts. A second examination, made two days later, showed essentially the same findings; in addition it was noted that the platelets numbered 76,000 per cubic millimeter, that 4.8 per cent of the red cells were reticulocytes and that the Schilling partition of the leukocytes showed 4 juvenile, 20 intermediate and no mature forms. Hematologic determinations made during the course of the disease are recorded in table 1. The erythrocyte sedimentation rate on October 29 was 48 mm. in one-half hour and 109 mm. in one hour. Roentgenograms of the long bones disclosed only normal findings; in particular there were no

TABLE 2.—*Chemical Findings Per Hundred Cubic Centimeters of Blood, Plasma and Serum*

		Plasma			Serum								
Date	Blood Sugar, Mg.	Van den Bergh	Bilirubin, Mg.	Fibrinogen, Gm.	Calcium, Mg.	Phosphorus, Mg.	Nonprotein Nitrogen, Mg.	Total Protein, Gm.	Albumin, Gm.	Globulin, Gm.	Euglobulin, Gm.	Pseudoglobulin I, Gm.	Pseudoglobulin II, Gm.
10/29/34	..	Direct negative Indirect +	0.31	.....	9.1	2.9	27.3	....	....	....	....	....	....
11/ 1/34	..	.....	....	.....	...	...	24.2	7.03	2.87	4.16	2.21	....	....
11/13/34	..	.....	....	.....	...	...	28.8	7.01	2.89	4.12	1.95	1.21	0.96
11/21/34	..	.....	....	.....	...	...	22.0	6.88	3.14	3.74	1.91	1.20	0.63
12/10/34	..	.....	....	.....	...	...	27.4	7.80	3.69	4.11	1.95	1.54	0.62
1/14/35	62	Direct +++ Indirect +	9.62	0.218	...	...	....	6.92	3.20	3.72	....	....	....
1/18/35	..	.....	....	.....	...	...	21.6	7.14	3.00	4.14	1.91	....	....

changes suggestive of leukemia, erythroblastic anemia or lead poisoning. Urinalysis revealed negative findings except for a trace of albumin. The reaction to 0.1 mg. of tuberculin given intradermally was negative, as was the Kahn reaction.

For the first four days the temperature ranged between 99.4 and 104 F., showing elevations in the morning and evening. Except for slight redness of both ear drums, no explanation of the fever was found. The blood picture remained unchanged; a fragility test revealed normal osmolar resistance of the red cells. Chemical studies revealed 27.3 mg. of nonprotein nitrogen per hundred cubic centimeters of whole blood; 9.1 mg. of calcium and 2.9 mg. of phosphorus per hundred cubic centimeters of serum, and 0.31 mg. of bilirubin per hundred cubic centimeters of plasma. The chemical findings are given in table 2.

The first clue to correct diagnosis came on the fifth day of hospitalization, when the possibility was entertained and investigated that the child might have been born in a country where kala-azar is frequent. It was then learned for the first time that she had been born in Sicily and had resided in the United States for six months only. In addition, it was ascertained that in Sicily the family had kept three dogs, with which the children played. This association is

mentioned specifically because investigators[5] have incriminated the dog as a possible agent in the transmission of the causative organism of kala-azar.

A diagnosis of kala-azar was adequate for explaining the splenomegaly, hepatomegaly, anemia, neutropenia, thrombopenia and fever. Erythroblastic anemia had been considered because of the race but was excluded by the blood picture and the roentgenograms. Gaucher's disease or Niemann-Pick disease did not account for the changes in the white cells or for those in the platelets. Blood smears had not revealed malarial parasites; moreover, the spleen seemed too large to be caused by malaria, considering the patient's age. Aleukemic leukemia seemed

Fig. 2.—Photomicrograph of a smear of material from a splenic puncture.

to be a likely diagnosis, but it was doubtful that pathologic cells could be absent and roentgen studies negative in a case of leukemia so far advanced as to produce the marked splenic enlargement.

The suspicion of kala-azar led to the immediate performance of Sia's precipitation test for euglobulin.[6] A positive reaction (4 plus) rendered diagnosis almost

5. Wenyon, C. M.: Transmission of Leishmania Infections, Tr. Roy. Soc. Trop. Med. & Hyg. **25**:319, 1932.

6. Sia, R. H. P.: Ray's "Hemolytic" Test in Kala-Azar, China M. J. **35**: 397, 1921; A Simple Method for Estimating Quantitative Differences in the Globulin Precipitation Test in Kala-Azar, ibid. **38**:35, 1924.

certain. The formaldehyde gel test also gave a positive result. Later a puncture of the spleen was done, and diagnosis was rendered absolute by the finding of numerous Leishman-Donovan bodies.

Specific treatment with an organic preparation of antimony was begun on October 2, the seventh day of hospitalization. At the suggestion of Dr. F. W. O'Connor, fuadin (sodium antimony biscatechol disulfonate) was selected for this purpose. It was administered by the intramuscular injection of a 6.3 per cent solution according to the following schedule:

Day	Dose
	Cc.
1	0.25
2	0.50
3	1.00
5	1.00
7	1.00
9	1.00
11	1.00
13	2.00

Thereafter 2 cc. was given every other day until the twenty-third day, when a total of 17.75 cc. had been injected. During this time the specific therapy was supported by nine blood transfusions.

The character of the fever before treatment with fuadin is shown in figure 3. There was no striking change during the first two weeks after therapy was started. During the third week, however, the elevations were neither so high nor so frequent, and on one day the temperature was normal. During the fourth and fifth weeks the temperature stayed practically within normal limits. There was also considerable reduction in the size of the spleen, which was appreciable as early as eight days after treatment with fuadin was begun. Subjective signs of improvement were apparent; the patient was brighter and more active and exhibited an interest in her toys.

The improvement, however, was only temporary. Although the temperature curve remained normal, the child again became irritable and cross, refused to eat her meals and occasionally had profuse diaphoresis. Transfusions were given repeatedly but without encouraging response. The hemoglobin content rose immediately after a transfusion but rapidly fell to the previous level. The erythrocyte count was proportionately low. The white cell count remained persistently low, seldom rising above 5,000 and occasionally dropping below 3,000 per cubic millimeter. Thrombocytopenia was likewise a constant finding.

During the first week of December the temperature was almost normal, the liver and spleen continued to decrease in size, and subjectively the patient did well. In the following week the temperature rose sharply to 104 F. and then continued to spike almost daily to 104 or 105 F. Although the ear drums were slightly injected, no sufficient cause for the hyperpyrexia was found on physical examination. Fuadin therapy was again instituted in the middle of the month, after a lapse of twenty days. At the onset 2 cc. was given intramuscularly every other day for one week. Because of troublesome vomiting the dose was decreased to 1 cc. for one week, to be increased to 1.5 cc. the following week. It is interesting to note that vomiting, which had been practically absent for the previous ten days, occurred on the day following the administration of fuadin. It is questionable whether this can be attributed to the fuadin itself, to the fever, to the mild infection

of the upper part of the respiratory tract or to all three. Toxic effects from the antimony had been watched for, and on this basis the dose of faudin was reduced to 1 cc.

The temperature curve showed considerable improvement after a week of treatment and rose only occasionally thereafter. However, the patient's general response was not so satisfactory as might be inferred from this. Toward the end of December the ear drums and nasopharynx again became injected. These signs subsided, only to recur after a short time.

Early in January 1935 the fuadin was discontinued entirely because of persistent vomiting. Food was given in small amounts only, and with great care and patience. The child became jaundiced and was pale, apathetic and lethargic. The temperature spiked irregularly each day while fuadin was administered and was persistently elevated when the drug was discontinued. A few days later the physical findings suggested that the infection of the upper part of the respiratory tract was as much responsible for the fever, anorexia and vomiting as the protozoan infection. There was a seromucoid discharge from the nose; the ear drums were dull, injected and bulging in the upper quadrants, and the pharynx contained mucus and moderately hypertrophied adenoid tissue. Myringotomy

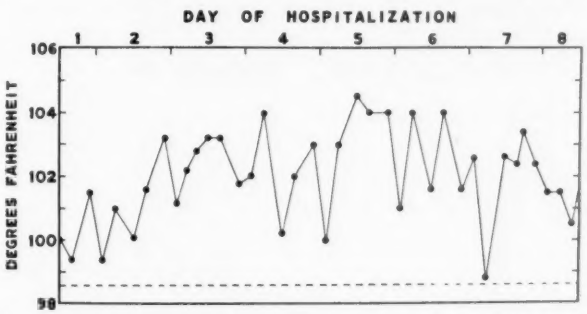

Fig. 3.—Chart showing the temperature curve of the patient previous to treatment with antimony.

of the left tympanic membrane released a moderate amount of thick serous exudate, which on culture produced Pneumococcus type XVIII. Again it was noted that the spleen was decreasing in size.

The otitis media continued, and a small area suggesting pneumonia appeared posteriorly at the base of the left lung. Occasionally the child was bothered by coughing and profuse diaphoresis. The temperature ranged between 100 and 102 F., the pulse was correspondingly high, and respirations, though not labored, were rapid, the rate sometimes being 60 to 70 per minute. Roentgen study of the chest at this time showed an increase in density in a wide strip between the right hilus and the diaphragm which was consistent with bronchopneumonia. On January 9 frank signs of pneumonia were elicited on both sides. Abdominal distention became troublesome, but insertion of a Levine tube for about thirty-six hours gave considerable relief. The jaundice noted previously was now intense, the level of serum bilirubin rising to 9.62 mg. per hundred cubic centimeters.

Despite the several transfusions which had been given (seventeen by the middle of January), the blood tended to revert to the original picture. On admission the hemoglobin content was 28 per cent, but it was maintained at about 50 per cent for the month of November. During the next month it

remained in the neighborhood of 65 to 75 per cent, only to show a sharp decline to between 40 and 50 per cent with recurrence of infection. The red cell count was proportionately low. Throughout the entire illness the platelet count was low. It was 76,000 on admission (the value accepted as normal according to the method used being about 600,000) and remained low until early in December, when it began to rise gradually, reaching a peak of 392,000 at the end of the month. With the added infection of the respiratory tract during January, thrombopenia recurred, the count falling sharply from 384,000 to 58,000 in one week. The white cell count also showed marked changes. It averaged about 4,000 and occasionally approached 6,500 per cubic millimeter. In the middle of January in the presence of purulent otitis media and pneumonia, the count dropped to

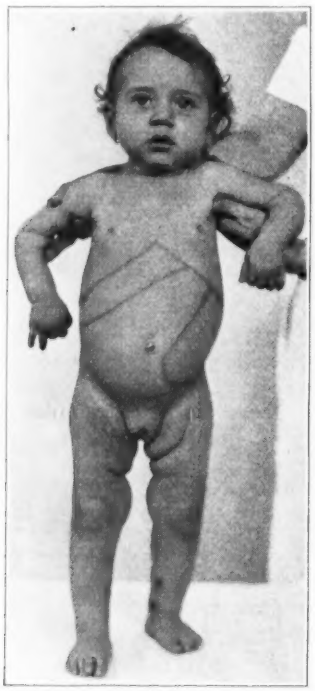

Fig. 4.—Photograph of the patient on Dec. 4, 1934, showing wasting and general debility.

2,900 per cubic millimeter. At this point pentnucleotide was given as suggested by Zia and Forkner,[7] who observed an elevation of the white cell count when this drug was given during periods of acute agranulocytosis occurring in the course of kala-azar infection. Pentnucleotide was administered intramuscularly, the dose being 0.35 Gm. given twice daily. The leukocytic response, however, was disappointing, and treatment was discontinued after a week's trial.

Late in January pus was found in the right naris; the right maxillary antrum was washed through the natural opening, but there was little exudate in the returned material. Culture of the nasal discharge yielded nonhemolytic Staphylococcus albus, Micrococcus catarrhalis and Streptococcus haemolyticus.

7. Zia, L. S., and Forkner, C. E.: The Syndrome of Acute Agranulocytosis and Its Occurrence as a Complication of Kala-Azar, Am. J. M. Sc. **188**:624, 1934.

The general condition became progressively worse. Loss of weight was marked; the weight was now 7,430 Gm. The skin was deeply jaundiced and hung in loose folds; muscle tone was extremely poor. The patient took both food and fluids poorly. Several times a day she was drenched in sweat; after diaphoresis she would be extremely drowsy and listless. The pneumonia became more extensive, and abdominal distention became troublesome. The size of the liver and of the spleen did not change. During this time the temperature was septic in type, varying daily from a normal level to 105 F. The leukopenia remained unchanged. On January 30, in an attempt to lower the temperature, fuadin therapy was resumed. The course was not altered.

On February 2 an erythematous, slightly bluish indurated area appeared on the lateral aspect of the left thigh, increased rapidly in size and in eight hours was approximately 12 cm. in diameter. Several similar but smaller areas, which appeared later on the lateral aspects of both legs, also increased rapidly in size. Blood culture at this time yielded Str. haemolyticus beta.

On the next day 150 cc. of citrated blood was given by transfusion, the father acting as donor, as he had done several times. Immediately after transfusion there was moderate epistaxis from the right nostril, followed in a short time by marked respiratory difficulty, mainly inspiratory. A solution of epinephrine hydrochloride gave slight relief, but after two or three hours the respiratory difficulty returned, there being marked inspiratory stridor and some cyanosis. More epinephrine hydrochloride was given, but without effect. A croup tent and an oxygen tent were tried, but the respiratory embarrassment became more acute.

Digital examination of the pharynx at this time revealed a boggy mass extending from the base of the tongue over the epiglottis and obliterating the normal angle of this region. Intubation was performed quickly, but the child gasped only a few times and died.

Necropsy was performed thirteen hours after death by Dr. Beryl Paige.

Postmortem Examination.—The more important postmortem observations indicated a general systemic infection. For the sake of brevity only the data having a direct bearing on the course of the disease or on the cause of death will be included in the protocol.

The body was emaciated, and the skin had an icteric tint.

The peritoneal cavity contained a few cubic centimeters of slightly bile-stained fluid. The spleen was greatly enlarged, the lower pole lying 10 cm. below the costal margin, on a level with the crest of the left ilium. The lower margin of the liver lay 4.5 cm. below the right costal margin and 3 cm. below the xiphoid process. In each pleural cavity was approximately 10 cc. of thin clear fluid.

The pleura covering each lung was free from exudate and adhesions. The upper lobe of the left lung was aerated throughout. The greater part of the left lower lobe was deep red and moderately firm, and on section the deep red surface was mottled with yellowish gray areas, indefinitely outlined. The posterior portions of the upper and the lower lobe of the right lung were deep red, and the upper lobe was firm. On section the cut surfaces of both lobes were red, and at the periphery of the upper lobe were grayish yellow regions. The main bronchi were congested. The lymph nodes at the hili of the lungs were dark red and measured up to 7 mm. in diameter. The nodes at the bifurcation of the trachea were similar in color but larger, measuring 2 cm. in greatest width.

The spleen weighed 295 Gm. (normal, 26 Gm.) and measured 10 by 8 by 4.5 cm. On the anterior surface was a shallow depression in which were delicate fibrous adhesions. The capsule was slightly thickened on the visceral surface

and on the posterior margin, but elsewhere it was smooth except for tiny depressions, pinpoint in size. The organ was purplish red and soft. On section the deep purplish red pulp was stippled with indefinitely outlined, yellowish gray flecks, measuring up to 2 mm. in width. No increase in connective tissue was evident. The lymph nodes at the hilus were brownish gray and measured 6 mm. in diameter.

The liver weighed 590 Gm. (normal, 304 Gm.) and measured 12 by 9.5 by 6 cm. The capsule was normal. The organ was pale brownish red and moderately soft. Beneath the capsule and on the cut surfaces were scattered purplish red to reddish gray areas 1 to 3 mm. wide, and pale gray linear markings surrounded the small bile ducts.

The alimentary tract was normal. In the mediastinal tissues about the esophagus were small hemorrhages. The lymph nodes at the lesser curvature of the

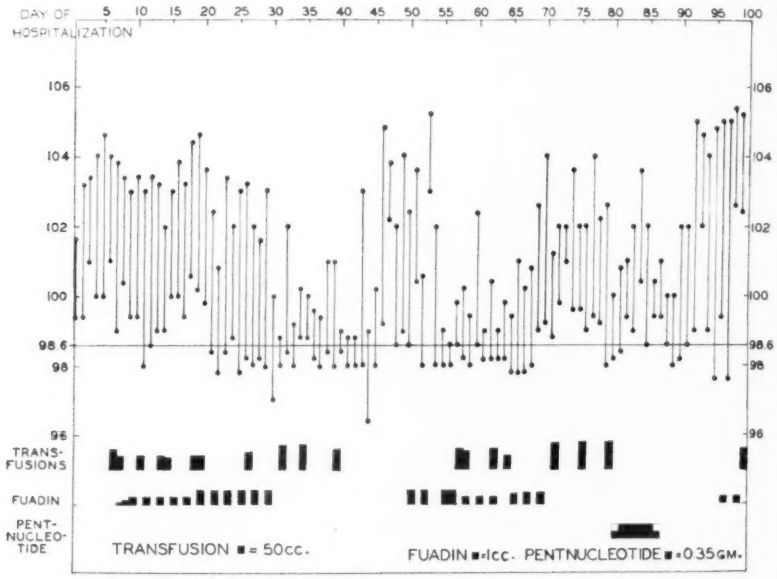

Fig. 5.—Temperature chart showing the high and the low points (F.) for each day throughout the illness. Transfusions and administration of fuadin and pentnucleotide are also represented.

stomach, at the hilus of the liver and about the head of the pancreas varied in color from grayish to yellowish brown and measured up to 3.5 cm. in diameter. At the root of the tongue, rising out of the vallecula, was a round grayish mass, without hemorrhage about it. The epiglottis was swollen and congested, and the aryepiglottic folds were tense and yellow. There was slight edema of the mucosa of the larynx but not of the vocal cords, and there were no ulcers.

The microscopic changes of interest were observed in the spleen, in the liver, in the epiglottis and in the lungs.

In the spleen the malpighian bodies were small, and in the centers of some of them were accumulations of reticulum cells filled with brownish pigment. In the pulp were many lymphocytes and myeloid cells, together with occasional

plasma cells and polymorphonuclear leukocytes. In addition there were scattered large basophilic elements with hyperchromatic nuclei. Erythrocytes were present in moderate numbers, and phagocytic cells filled with yellow pigment were frequent. In the sinuses were occasional large mononuclear cells. Iron-containing pigment was demonstrable in cells in the pulp and in the sinuses. Smears made from the spleen and sections prepared with Giemsa stain failed to show Leishman-Donovan bodies.

In the portal spaces and surrounding the margins of the hepatic lobules was a heavy cellular infiltration composed of polymorphonuclear leukocytes, lymphocytes and large mononuclear cells. The regional hepatic cords were atrophic, and there was proliferation of the small bile ducts. In the remainder of the lobules the liver cells contained small fat vacuoles. Small and large bile plugs distended some of the bile radicles. The Kupffer cells were swollen. In the phagocytes in the portal spaces, in the Kupffer cells and in some of the hepatic cells were deposits of iron. No Leishman-Donovan bodies were noted in direct smears from the liver or in sections.

The entire mucous membrane of the epiglottis was filled with polymorphonuclear leukocytes and erythrocytes, and the acute inflammation extended anteriorly to the root of the tongue and posteriorly into the aryepiglottic folds. In the superficial portions there was necrosis of the normal structures and of the cells of the exudate, and streptococci were present in huge numbers.

The lungs showed changes characteristic of bronchopneumonia. No Leishman-Donovan bodies were observed.

The architectural markings of the lymph nodes were maintained, though lymphoid follicles were small. Among the lymphocytes were plasma, myeloid, polymorphonuclear and large mononuclear cells, and the sinuses were filled with leukocytes, both polymorphonuclear and mononuclear. In the macrophages was iron-containing pigment.

COMMENT

Kala-azar is a clinical rarity in the United States. Once suspected, however, the diagnosis may be tentatively confirmed by the performance of Sia's precipitation test for euglobulin.[6] Sia has demonstrated that the severity of the infection may be judged from the rapidity and the amount of the precipitation of euglobulin; in the case reported there was heavy precipitation after one minute. Results of the formaldehyde-gel test, if positive, also suggest kala-azar. Existence of the disease is positively established by finding Leishman-Donovan bodies. In this case they were recovered from the spleen (fig. 2); splenic puncture was made with no untoward results by aspirating at the most prominent site with the usual blood needle.

The temperature curve during the first week of hospitalization, when no treatment was given, is shown in figure 3. It illustrates the irregular elevations, occurring twice daily, commonly seen with this disease. Administration of fuadin served to reduce the hyperpyrexia and, if persisted in, caused a return to a normal level; shortly after administration of fuadin was stopped, however, the temperature again rose. The high elevations were usually accompanied by debilitating diaphoresis, anorexia

and easy fatigability. I believe that if possible the temperature should be controlled; judgment as to the continued administration of fuadin, however, must be tempered by consideration of untoward symptoms such as the severe vomiting experienced by this patient.

Throughout the illness the blood picture was characterized by anemia, neutropenia and thrombopenia. Despite repeated transfusions (2,640 cc. of blood was given in nineteen transfusions over a period of three months) the blood picture failed to return to normal. Response of the leukocytic series to the severe infections, kala-azar and bronchopneumonia, was extremely poor. Attempts to stimulate leukocytic production by administration of pentnucleotide, which Zia and Forkner [7] have used with success in cases of kala-azar complicated by severe leukopenia, did not alter the picture. The polymorphonuclear-lymphocyte ratio was low in the beginning and rose only in the last weeks of life. Mononuclears were not present in remarkable numbers. Normoblasts were observed only occasionally. There was no eosinophilia. The reticulocyte count was elevated during the early period of hospitalization; its maintenance at high levels during December and January may possibly be explained as due to hematopoietic response of the bone marrow to transfusions. The platelet count was low throughout the entire course. Changes in the character of the erythrocytes were practically constant; these consisted in anisocytosis, poikilocytosis, achromasia and polychromatophilia. The color index remained below 1 when the blood elements were at an extremely low level; as the hemoglobin content and the red cell count became elevated, the color index sometimes became greater than 1. Clot retraction was normal, and tests for hemolysis gave negative results.

The determinations of blood chemistry are recorded in table 2. The high euglobulin value was characteristic and agreed with analyses reported by Ling.[8] The absolute decrease in serum albumin and the absolute increase in serum globulin were in accord with observations on patients with kala-azar reported by Sia and Wu.[9] Through Dr. Warren M. Sperry a series of analyses for free and combined cholesterol was obtained. These are recorded in tables 3 and 4. The total cholesterol concentration and the ratio of combined cholesterol to free cholesterol were consistently low. I am not aware that the latter finding in kala-azar has received comment, but the analyses were in agreement with figures reported by Ginandes [4] for his patient. Several investigators (see

8. Ling, S. M.: Distribution of Protein Fractions in the Serum of Kala-Azar Patients, Proc. Soc. Exper. Biol. & Med. **27**:247, 1930.

9. Sia, R. H. P., and Wu, H.: Serum Globulin in Kala-Azar, China M. J. **35**:527, 1921.

Epstein[10] for a summary of the literature) have reported marked decreases in the ratio of combined cholesterol to free cholesterol with certain diseases of the liver. Sperry[11] has emphasized the relative constancy of the ratio in health; with the method[12] employed in this laboratory the range of variation was much less than has been reported by most investigators. With few exceptions, values below normal were encountered only in the presence of hepatic disease or acute infection or both. It is impossible to state whether the virtual disappearance of cholesterol esters (*Estersturtz*[13]) noted for my patient in the third determination (table 3) is related in a general way to the infection or directly to invasion of the liver with Leishmania. It is of interest that the ratio rose markedly with the response to treatment with the antimony compound but at no time approached the lower limit of normal (2.2).

TABLE 3.—*Cholesterol per Hundred Cubic Centimeters of Serum*

Date	Total, Mg.	Free, Mg.	Combined, Mg.	Ratio
10/29/34	75.3	64.0	11.3	0.18
11/13/34	71.5	54.4	17.1	0.31
11/21/34	62.5	55.8	6.7	0.12
12/10/34	116.1	62.5	53.6	0.86
1/14/35	104.8	80.6	24.2	0.30

TABLE 4.—*Postmortem Analyses of Liver*

Cholesterol	Moist Liver, Percentage	Dry Liver, Percentage
Total	0.304	1.47
Free	0.290	1.40
Combined	0.014	0.07

It is notable that the ratio in the case reported was strikingly low at a time when the bilirubin content of the plasma was only 0.3 mg. per hundred cubic centimeters.

The tissue cholesterol values are recorded in table 4, although the significance of these figures cannot be evaluated at the present time.

The drug selected for the treatment of this patient deserves brief comment. Fuadin, or sodium antimony biscatechol disulfonate in a 6.3 per cent solution, was used; this preparation was formerly known

10. Epstein, E. Z.: The Cholesterol Partition of the Blood Plasma in Parenchymatous Diseases of the Liver, Arch. Int. Med. **47**:82 (Jan.) 1931.

11. Sperry, W. M.: The Relationship Between Total and Free Cholesterol in the Human Blood Serum, J. Biol. Chem. **114**:125, 1936.

12. Schoenheimer, R., and Sperry, W. M.: Micromethod for Determination of Free and Combined Cholesterol, J. Biol. Chem. **106**:745, 1934.

13. Thannhauser, S. J., and Schaber, H.: Ueber die Beziehungen des Gleichgewichtes Cholesterin und Cholesterinester im Blut und Serum zur Leberfunktion, Klin. Wchnschr. **5**:252, 1926.

as neo-antimosan. Various organic compounds of antimony have been developed, chiefly in India, for treating leishmaniasis, an attempt being made to diminish toxicity while retaining therapeutic action. Fuadin was developed in Egypt for treatment of bilharziasis; it has not yet received extensive trial in the treatment of kala-azar. It was recommended because of its low toxicity and because it is available in the United States. I believe that the drug was effective in this case because of the subjective improvement, the decrease in the size of the spleen and the decline of the fever and particularly because autopsy failed to show any residuum of protozoan infection. Failure to secure continued improvement seems to be explained by the secondary infection.

SUMMARY

A case of kala-azar occurring in a child is placed on record. It is the fifth case to be reported in the American literature.

The chief symptoms of the disease are splenomegaly, hepatomegaly, anemia, neutropenia, thrombopenia and fever. Sia's precipitation test for euglobulin and the formaldehyde-gel test, if results are positive, assist in establishing the diagnosis. Demonstration of Leishman-Donovan bodies renders the diagnosis absolute.

The cytologic and chemical studies of the blood are recorded.

Fuadin, an antimony preparation, was used in treatment. This drug apparently controlled the protozoan infection.

The important postmortem observations are described.

360 State Street.

PRIMARY PROLIFERATIVE PULMONARY ARTERIOLAR SCLEROSIS

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AND
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Primary proliferative pulmonary vascular sclerosis is rare. Brenner,[1] in an exhaustive study of the pathology of the vessels of the pulmonary circulation and with an excellent review of the literature, could find but 16 well described cases, including 1 of his own, that could be accepted without reserve. In all other cases appeared some factor, such as chronic cardiac or pulmonary disease, that was thought capable of causing secondary sclerosis, either severe or in mild form. It seems obvious that the latter cases fall into that group reported in the literature as cases of Ayerza's disease [2] or syndrome, as in all of these the condition was obviously secondary vascular sclerosis of the pulmonary artery. Without exception it was associated with chronic bronchopulmonary or cardiac disease.[3] This is true also of the cases recently described by Kaump and Dry.[4] MacCallum [5] found but 1 case of primary proliferative sclerosis of the pulmonary artery in reports of 12,000 autopsies. Our case is the only one disclosed in 2,707 consecutive necropsies at the Children's Memorial Hospital. Mallory [6] recently reported a typical case almost identical with the one presented here.

REPORT OF A CASE

Clinical History.—W. M., a boy, was admitted to the Children's Memorial Hospital on Nov. 27, 1937, at the age of 10 years and 3 months. The chief complaint was attacks of unconsciousness which had begun during the previous

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From the pathologic and cardiac departments of the Children's Memorial Hospital and the Otho S. A. Sprague Memorial Institute.

1. Brenner, O.: Pathology of the Vessels of Pulmonary Circulation, Arch. Int. Med. **56**:976 (Nov.) 1935.

2. (*a*) Ayerza, L.: Semana méd. **2**:386 (Aug. 13) 1925. (*b*) Cheney, G.: Am. J. M. Sc. **174**:34 (July) 1927.

3. Parker, F., Jr., and Weiss, S.: Am. J. Path. **12**:573 (Sept.) 1936.

4. Kaump, D. H., and Dry, T. J.: Pulmonary Arteriolar Sclerosis: Clinicopathologic Study, Arch. Int. Med. **61**:1 (Jan.) 1938.

5. MacCallum, W. G.: Bull. Johns Hopkins Hosp. **49**:31-38 (July) 1931.

6. Cor Pulmonare, Cabot Case 23511, New England J. Med. **217**:1045 (Dec. 23) 1937.

summer and had occurred at intervals up to the time of the child's admission. The mother thought that he had had about a dozen attacks. The spells occurred usually when he was playing; none had occurred at night. The patient's first symptom consisted of choking and inability to get his breath. He pulled at his clothing and struggled for air, finally losing consciousness and falling. The skin became blue, and the extremities were cold. Each attack lasted for only a few moments. Vomiting frequently followed, and the boy often slept for half an hour or so afterward. He had four such fainting spells in the two weeks previous to admission.

The child had had difficult breathing on exertion during the past year. He had scarlet fever at the age of 3½ years, measles at 4 years and pertussis at 9 years. The dyspnea was first noted shortly after the attack of pertussis. There had been no articular pains or other evidence of rheumatic fever. The tonsils had been removed one year before the boy's admission to the hospital. The mother and four other children were well. The father gave a history of heart trouble beginning six years previously.

Physical examination revealed a poorly developed and poorly nourished boy, not acutely ill though moderately dyspneic. The heart was somewhat enlarged to percussion. The apex thrust was palpated in the fifth interspace, about 1 inch (2.5 cm.) to the left of the midclavicular line. There was a marked gallop rhythm at the apex. At the pulmonary area a thrill was palpable, and a long diastolic murmur was audible here. The systolic blood pressure was 84 and the diastolic 72. The edge of the liver was palpable about 1½ inches (3.8 cm.) below the costal margin in the nipple line.

The white blood cell count on the patient's admission was 15,000 per cubic millimeter; it varied between this figure and 28,000 during his stay in the hospital. The urine was normal, the Kahn reaction negative and the Mantoux reaction positive. The rate of sedimentation of the red blood cells was normal. A roentgenogram which had been obtained on April 22 showed slight cardiac enlargement together with unusual prominence of the pulmonary conus. On a later roentgenogram, obtained after the boy's admission to the hospital, there was a similar contour, but the shadow of the heart was considerably larger than on the previous examination (fig. 1). On the electrocardiogram there was marked right axis deviation. The PR interval was 0.2 second. The QRS complex in lead II was diphasic, the upward phase being 12 mm. and the negative phase 10 mm. The T wave was inverted in leads II and III.

On December 5, after having been relatively comfortable, the patient had a syncopal attack with mild twitching of the extremities. Breathing was rapid; the extremities became cold; there was intense cyanosis, and cold perspiration bathed the forehead. The heart rate was 160; the pulse was imperceptible at the wrist. The duration of the attack was twenty-five minutes. After this episode the boy again became fairly comfortable, though there was slight dyspnea.

On the afternoon of Jan. 11, 1938, the child complained of pain in both arms and in the epigastrium. A few hours later he suddenly became intensely cyanotic; respirations became shallow and slow, and death ensued.

There was much speculation as to the diagnosis. The physical findings were difficult to harmonize with either rheumatic or congenital heart disease. The progressive enlargement of the heart suggested continued damage to the myocardium, such as occurs with rheumatic carditis, though there was no history of rheumatic infection. The location and timing of the murmur were not thought to be compatible with involvement of either the mitral or the aortic valve. The loud diastolic murmur and the thrill in the second left interspace did not suggest

any type of congenital cardiac defect with which we were familiar. The diphasic QRS complex in the electrocardiogram was strongly indicative of congenital heart disease.[7] The prominent pulmonary conus suggested pulmonary vascular sclerosis, though we hesitated to make this diagnosis because of the absence of polycythemia and constant cyanosis, which have been emphasized as characteristic of the Ayerza syndrome.[2a] We were uncertain as to whether the syncopal attacks were circulatory in origin or possibly epileptiform.

Postmortem Examination.—This was performed two hours after death.

Gross Study: The body was well developed but poorly nourished. The weight was 47½ pounds (21.4 Kg.) and the length 127 cm. There was a paucity of subcutaneous fat, and there was marked generalized pallor; otherwise the superficial topography was essentially normal.

The abdominal cavity contained about 50 cc. of thin straw-colored fluid. The viscera had their normal anatomic positions. The retroperitoneal tissues from the diaphragm to the true pelvis were markedly edematous and friable. This was also true of the mesentery and of the serosal surfaces of the intestines.

The liver was enlarged, the edge extending 4 or 5 cm. below the right costal margins; it was dark reddish purple to brown, with irregular mottled regions

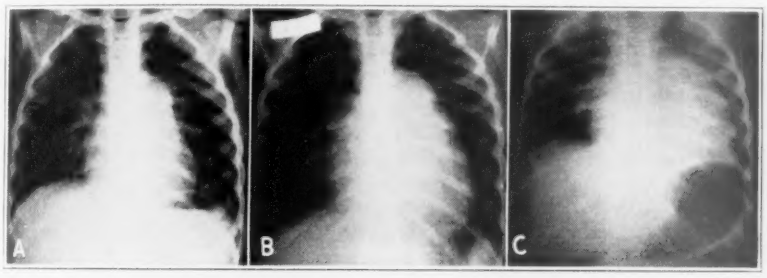

Fig. 1.—Roentgenograms taken at a distance of 6 feet. *A*, made on April 22, 1937, shows slight cardiac enlargement with unusual prominence in the region of the pulmonary conus. *B*, made on Nov. 27, 1937, shows marked enlargement of the heart with the same prominence in the region of the pulmonary conus. *C*, made one hour after death (Feb. 11, 1938) shows further enlargement of the cardiac shadow.

of yellowish red. It was firm and cut with increased resistance, and beneath its capsule were focal regions of hemorrhage. The intrahepatic blood vessels were intensely engorged and widely dilated. In general, this organ had the appearance of a "nutmeg" liver. Fatty changes were grossly evident in the central portions of the lobules. The weight was 850 Gm. The gallbladder was unchanged.

The spleen and the pancreas were unchanged; they weighed 80 and 25 Gm., respectively.

The gastrointestinal tract revealed no unusual pathologic changes.

In the kidneys, adrenal glands, renal pelves, ureters and urinary bladder there was no variation from normal except intense passive hyperemia. The kidneys weighed 160 Gm. together, the adrenal glands, 6 Gm.

The thoracic cavity contained no free fluid, exudate or adhesions; no evidence of tuberculosis was present. Both lungs were partially collapsed, air containing

7. Katz, L. N., and Wachtel, H.: Am. Heart J. **13**:202 (Feb.) 1937.

and reddish gray and had a somewhat soft, velvety texture. In the posterior and basilar portions of both lower lobes were small focal atelectatic regions which varied from red to purple. On section both lungs were deep saffron, and the pulmonary vessels and the bronchi were equally distinctly prominent. The entire pulmonary arterial system was widely dilated (fig. 2). The main branches of the pulmonary artery were so dilated that they had the size normally seen in the pulmonary artery proper, and the smaller branches stood out as thick-walled tubes. The trachea was partially filled with thick mucoid blood-tinged exudate. The left main bronchus was completely occluded by a plug of this material, which

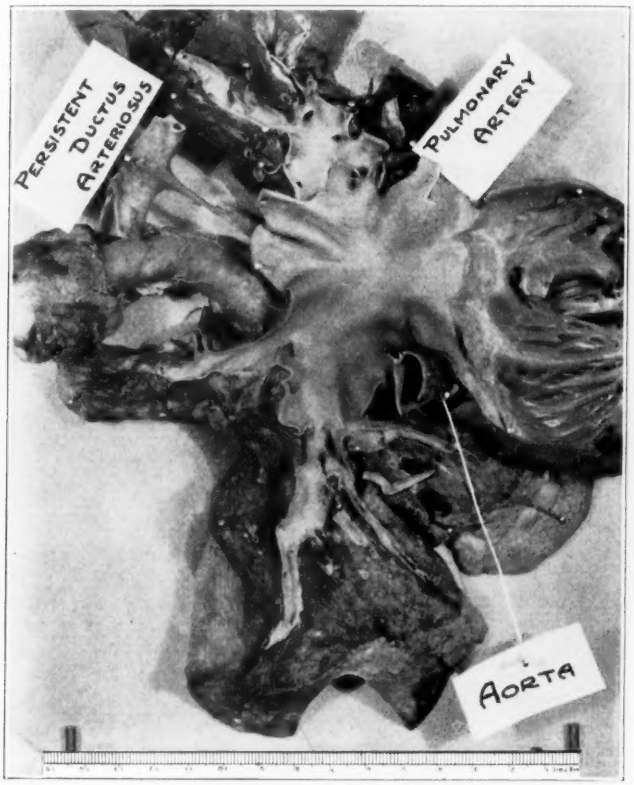

Fig. 2.—Photograph of the opened pulmonary artery and its branches, showing marked dilatation but no obstruction in the larger portions.

was easily removed. The mucosa of the trachea was intensely hyperemic, but no ulcerations or fibrin was present.

The heart (fig. 3) was markedly enlarged, particularly its right chambers, measuring 14 cm. across its widest portion, as compared with 20 cm. for the diameter of the chest at the same level. There were marked dilatation and hypertrophy of the right ventricle and right auricle. The musculature of the myocardium was pale but showed no pathologic change. The heart weighed 395 Gm. (normal weight, 125 Gm.). The myocardium of the left ventricle was 1 cm. thick and that of the right was 1.2 cm. The pulmonary artery was widely

dilated, its circumference being 7 cm.; that of the aorta was 3.5 cm. The right and the left pulmonary artery measured 3.2 and 3 cm., respectively, in circumference. When the heart was opened all the valves appeared normal and competent except the pulmonary and the tricuspid. These were dilated, their cusps failing to approximate each other by 0.5 cm. The pulmonary valve measured 6.8 cm. in circumference, the aortic, mitral and tricuspid valves, 3.4, 3.3 and 4.1 cm., respectively. The foramen ovale was closed. There was no interauricular or interventricular septal defect. Dissection of the coronary vessels revealed no gross abnormalities. The pericardial cavity contained 100 cc. of straw-colored

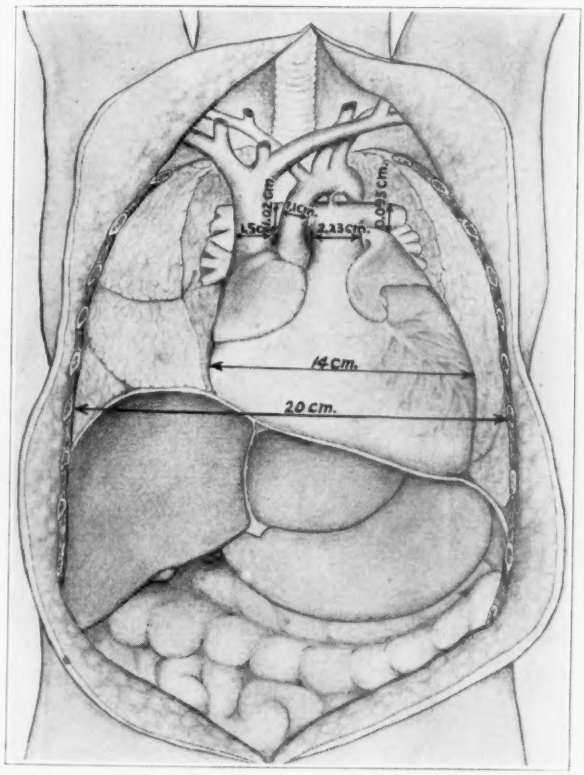

Fig. 3.—Artist's drawing, showing hypertrophy of the right ventricle and marked dilatation of the pulmonary artery and its branches (appearance when the chest was opened). Measurements represent diameters.

fluid; its surfaces were everywhere smooth and glistening. The thymus and thyroid gland, grossly and when sectioned, were unchanged.

Bacteriologic Study: Cultures of the heart's blood and of peritoneal, spinal and pericardial fluid were negative after seven days of continuous incubation.

Histopathologic Study: Sections of the pancreas, thymus and thyroid were normal; the blood vessels were unchanged.

The appendix vermiformis showed minimal chronic inflammatory changes and chronic passive hyperemia.

In multiple sections of the myocardium, made through both ventricles and auricles, there were no changes of the blood vessels. There was moderate hypertrophy of the muscle fibers in all sections; this was most marked in the right ventricle and auricle. Replacement fibrosis was not seen. Cellular infiltration was absent.

Throughout the spleen there was a moderate increase in the fibrous connective tissue. It was engorged with blood. The blood vessels were normal.

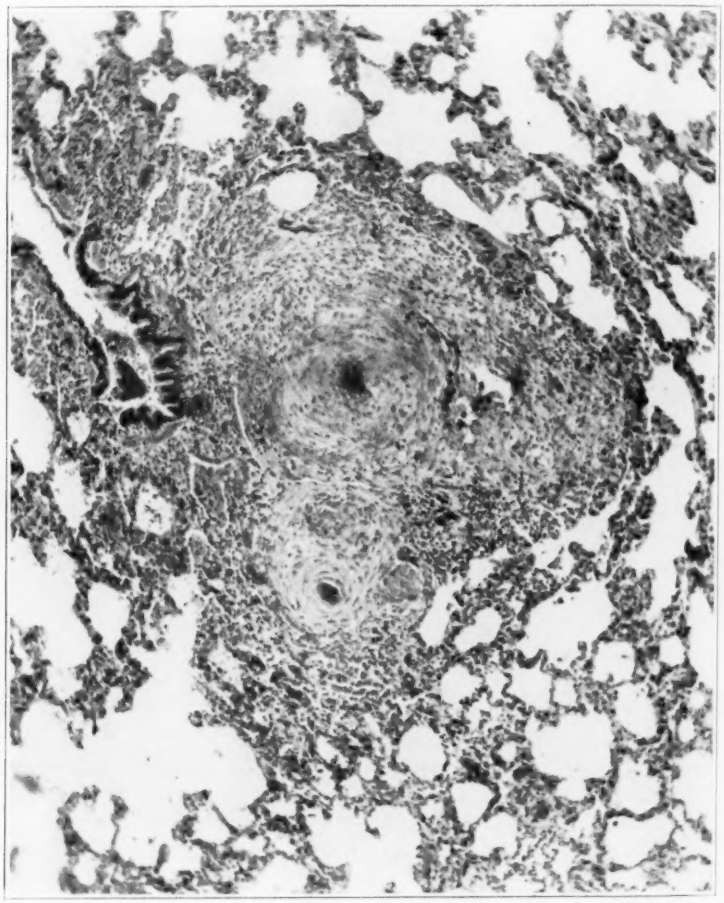

Fig. 4.—Primary obliterative pulmonary arteriolar sclerosis. Recent thrombi are visible in the pulmonary arterioles; there is emphysema. Note the absence of indurative disease of the lung parenchyma. Hematoxylin and eosin stain; × 70.

The liver showed intense chronic passive hyperemia with necrosis and hemorrhage about the efferent veins; a narrow zone of fat-containing liver cells surrounded each necrotic area (scarlet red stain). There were pale-stained liver cells about the afferent veins and the hepatic arteries. The walls of the blood vessels were normal.

In the kidney there was intense chronic passive hyperemia. The capillaries of the glomeruli were distended with blood. There was a small amount of coagulated fluid in Bowman's capsule, and an occasional hyaline cast was noted in the tubules. In the tubular epithelium there was cloudy swelling to a moderate degree. The veins were all engorged with blood, but their walls, like those of the arteries, contained no microscopic change.

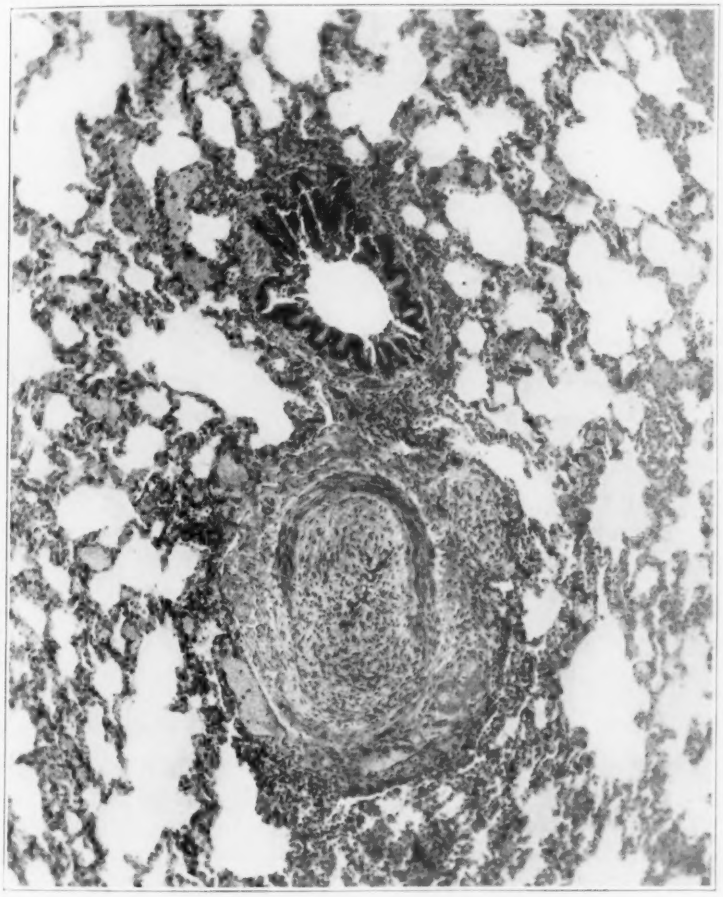

Fig. 5.—Primary proliferative arteriolar sclerosis with complete occlusion of the lumen of the arteriole. Emphysema and minimal edema of the alveoli are apparent. Hematoxylin and eosin stain; × 60.

Multiple sections were taken from all lobes of the lungs at various places (paraffin and pyroxylin sections stained with hematoxylin and eosin, Mallory's, aniline blue and Verhoeff's elastic tissue stain [figs. 4-7]). The pleura was uniformly thin. There were both emphysema and atelectasis. The alveolar spaces were free from exudate except in the sections taken from the posterior and basilar portions of both lower lobes. Here many of the alveoli contained coagulated edematous fluid and free blood. In a few other places, scattered widely through-

out, were focal areas of round cell infiltration, but no polymorphonuclear cells were seen. Deposition of pigment was not significant. Otherwise the lung parenchyma contained little microscopic change.

The pulmonary artery and its branches, aside from the marked dilatation of all the larger branches (fig. 2), presented little of significance. The intimal layers were smooth, with no gross or microscopic evidence of atheromatous changes.

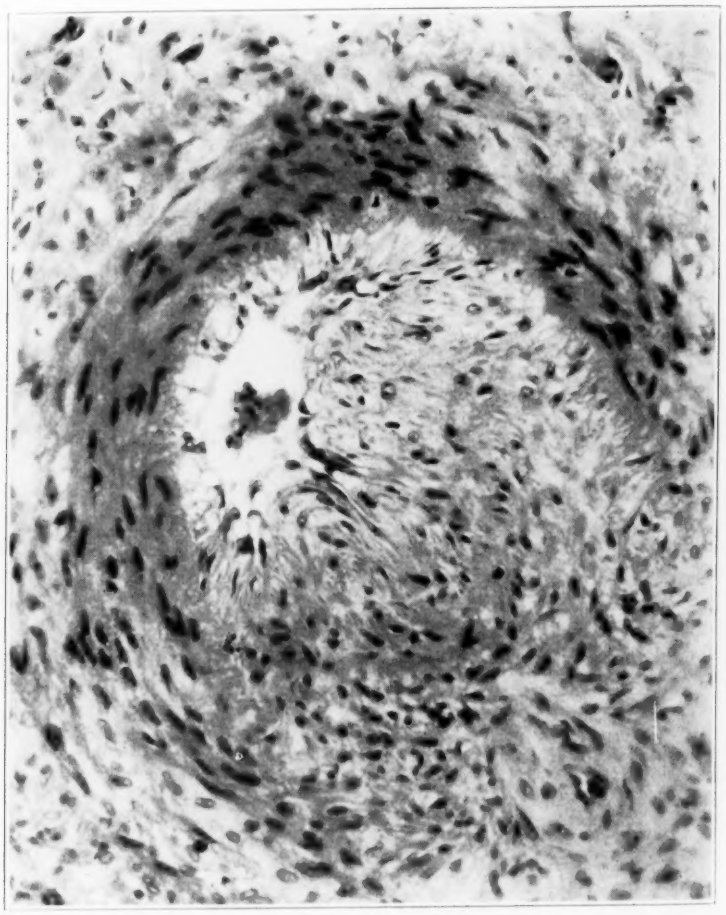

Fig. 6.—Primary proliferative pulmonary arteriolar sclerosis. Hematoxylin and eosin stain; × 275.

However, there was a minimal increase in the fibrous tissue of the media, although the elastic fibers were intact.

In the smaller pulmonary arteries, which were 1 or 2 mm. in diameter, the only changes were a moderate proliferating type of reaction in the intimal portions, a slight degree of change in the media and moderate fibrosis of the adventitia. The tissue that produced the intimal proliferation was an extremely loose network with spaces filled with large cells in which the cytoplasm was finely vacuolated. The supporting tissue was made up of elongated cells similar to

those just described. In none of these vessels was there breaking of the elastica of the intima or irregularity of the external elastica. However, for the most part the media and the adventitia were normal, there being no change of the muscle or elastica. There was no perivascular wandering cell infiltration which could be suggestive of syphilis, nor was there other evidence of this disease.

In the still smaller branches of the arteries—the arterioles which measured less than 1 mm. in diameter—the building up of new tissue in the intima was

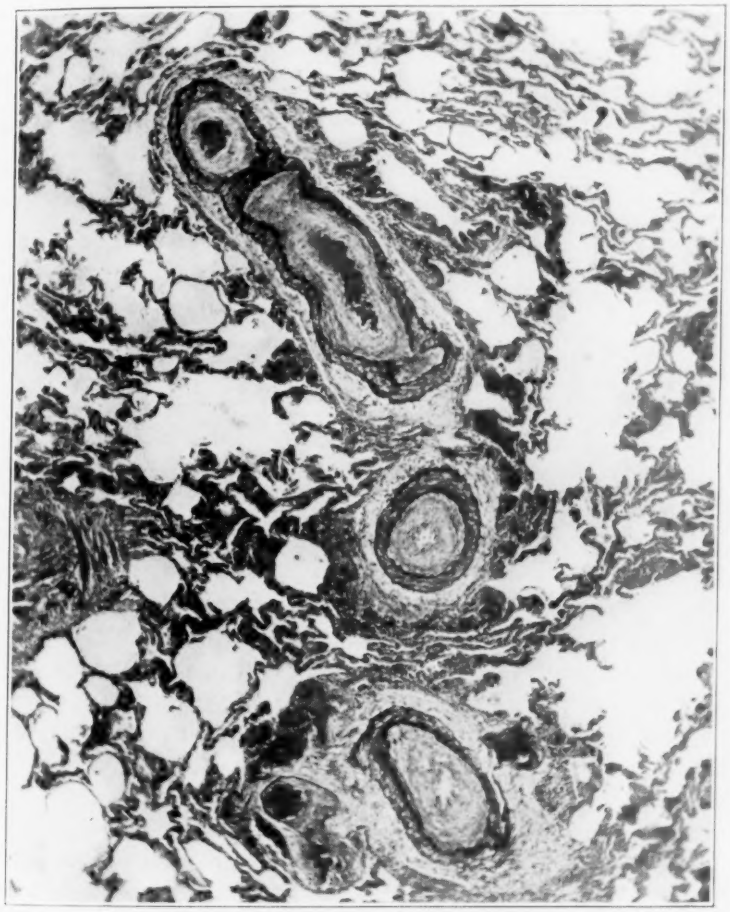

Fig. 7.—Primary proliferative arteriolar sclerosis. The intact elastica is illustrated. Verhoeff's elastic tissue stain; × 60.

seen in every stage, ranging from slight thickening of the intimal layer to complete and solid occlusion of the lumen with the disappearance of the endothelial lining cells. In the intermediate stages (represented in most of these arterioles), in which the lumen was still evident, the endothelial cells were crowded together and thrown up into folds. Frequently the red cells in the lumen were plainly stagnant and the corpuscles partly disintegrated. Most often, however, there was a homogeneous or hyaline thrombotic mass which was becoming recanalized by

newly formed capillaries. Sometimes these vessels could be seen in the thick intimal layer which caused the obstruction. A few of their arterioles were so completely obliterated and hyalinized that they were difficult to identify except by their location and their relation to the smaller bronchi.

The veins and venules for the most part were normal. A few were distended with blood.

The aorta was normal.

Anatomic Diagnosis: There were primary proliferative pulmonary arteriolar sclerosis; marked hyperplasia of the pulmonary artery and its branches; hypertrophy of the myocardium of the right ventricle; emphysema of the lungs; disseminated focal hemorrhages into the alveoli of the lungs; dilatation of the right auricle of the heart; chronic passive hyperemia of the liver ("nutmeg"), pancreas, kidneys and bowel; fatty changes of the liver; disseminated focal atelectasis of the lungs.

COMMENT

Primary proliferative pulmonary arteriolar sclerosis is essentially a disease of the branches of the pulmonary arteries in which the thickening of the intimal layer reduces the lumen to an extremely minute canal or completely obliterates it by proliferation. In order to justify a diagnosis of primary proliferative pulmonary sclerosis all factors thought to cause secondary sclerosis must be absent. Marked hypertrophy of the right ventricle of the heart is necessary. Systemic vascular sclerosis is still a point of controversy among investigators. Finally, changes in the pulmonary vessels must not be due to specific infection, such as syphilis, rheumatism or tuberculosis, though obviously inflammatory changes are not excluded as long as their origin is unknown.

Brenner [1] gave criteria by which it is possible to diagnose the disease clinically, though the final diagnosis must depend on the microscopic picture: They are (1) severe cyanosis and edema with comparatively little dyspnea (the cyanosis may be slight and the edema absent); (2) clinical and electrocardiographic evidence of hypertrophy of the right ventricle but not of the left; (3) an accentuated pulmonary second sound, perhaps with a pulmonary diastolic murmur but without murmurs indicative of valvular or congenital cardiac disease; (4) no clinical or roentgen evidence of chronic pulmonary disease; (5) roentgen evidence of enlargement of the right side of the heart with prominence of the pulmonary artery and conus of the right ventricle but with a normal shadow of the left auricle, and (6) no evidence of syphilis, rheumatism, tuberculosis or other infection affecting the heart or lungs.

The resulting symptoms are about the same in all cases. The anatomic changes throughout the body are similar, but uncertainty exists as to the cause. Many investigators have offered suggestions, all of which have proved to be erroneous or inadequate.

The symptoms of this disease are chiefly those of right ventricular failure, for which no adequate cause can be found. Dyspnea is characteristically slight and orthopnea usually absent. This is in striking

contrast to the severity of the cyanosis and edema of most patients with right ventricular failure. Cyanosis is usually intense but not quite as deep as with congenital heart disease; it may be present only on exertion or it may be entirely absent. Polycythemia is a variable finding, and the red cell count may be normal. Edema is even more prominent than cyanosis. It is sometimes the leading symptom and may be associated with ascites and pleural effusion. Edema may be absent, however. Palpitation is frequent. Hypercyanotic angina is mentioned, and pain may radiate down the arms instead of deeply into the chest. Neurologic symptoms, such as vertigo, headache, blurred vision, somnolence and syncope, may be associated with the cyanosis. Vomiting, abdominal pain, muscular rigidity and incontinence may accompany an attack of syncope.

On physical examination there is no direct evidence of chronic pulmonary disease, but pleural effusion may occur as part of the generalized anasarca. Eppinger and Wagner [6] stressed the absence of hyperemia of the lungs. The heart is always enlarged to the right. The pulmonic second sound is usually greatly accentuated and may be followed by a soft diastolic murmur due to functional incompetence of the pulmonary artery. There may be a soft pulmonary and apical systolic murmur without evidence of organic disease. In the electrocardiogram evidence of right axis deviation is usual. Roentgenograms reveal varying degrees of cardiac enlargement with a prominence in the region of the pulmonary conus. The left auricle is normal in the oblique view. Excessive pulsations of the hilar shadows may be noted, being due to functional pulmonary incompetence. The blood pressure is usually normal.

Duration of symptoms in the reported cases varies from five months to five years. The average duration is less than two years. Treatment is ineffective, and retrogression is continuous.

In the reported cases the age of incidence varied from 6 weeks to 74 years, but in most of the cases involvement occurred in childhood, adolescence or early adult life.

SUMMARY

Primary proliferative pulmonary arteriolar sclerosis is extremely rare, but 16 cases having been previously reported in the literature. The case here reported, that of a boy 10 years of age, is typical in its clinical and anatomic features. As with all other recorded cases, no explanation has been found as to what caused this extreme degree of proliferative occlusion of the pulmonary arterioles without similar changes in other parts of the circulatory system.

Drs. Wells, Humphreys, Apfelbach and Hibbs furnished aid and suggestions and Mr. Charles Zinser made the anatomic drawing.

Progress in Pediatrics

SULFANILAMIDE AND RELATED COMPOUNDS

A REVIEW OF THE LITERATURE

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AND
JAMES Q. HARALAMBIE, M.D.
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In no branch of medicine do sulfanilamide and its derivatives occupy a position of greater importance than in treatment of the infections occurring during infancy and childhood. Although these preparations are comparatively new, the literature pertaining to their use has already become voluminous and is international in its scope. The clinical and laboratory investigations pertaining to this drug have far exceeded those of any other pharmaceutic preparation in this generation. At present there is considerable confusion, as in some instances several names have been used for the same compound or the same name has been used for several related compounds. Adding to this confusion is the frequent reference to these chemicals in complicated and variously written chemical formulas, which is bewildering to one not thoroughly versed in the terminology of organic chemistry. The variety and multiplicity of the toxic manifestations of the different compounds add further to the confusion.

Because of these facts and because of the great part that sulfanilamide is playing in present day therapeutics, we thought it would be appropriate to collect and evaluate reports and to present a review of the literature, pointing out the beneficial as well as the toxic properties of the sulfanilamide compounds. Sulfanilamide comes closer to being a body antiseptic for certain pathogenic organisms than any other substance known.

HISTORY

Gelmo [1] in 1908, working on azo dyes, was the first to mention the paraaminosulfonamide compounds. His interests being industrial, no clinical application was made of these compounds. During the subsequent

From the Children's Memorial Hospital and the Otho S. A. Sprague Memorial Institute.

1. Gelmo, P.: Ueber Sulfamide der *p*-Amidobenzolsulfonsäure, J. f. prakt. Chem. **77**:369, 1908.

years a number of compounds of azo dyestuffs with sulfonamide were made. Their bactericidal powers were first conceived by Eisenberg.[2] From these investigations sprang scarlet red, included in "New and Nonofficial Remedies" by the American Medical Association in 1912 as a valuable drug in the treatment of chronic ulcers and wounds. In 1932 Mietzsch and Klarer[3] synthesized the original prontosil (the hydrochloride of 4-sulfamido-2′,4′-diaminoazobenzene), a red powder 0.25 per cent soluble in water. Domagk[4] in the same year pointed out the antistreptococcic action of certain azo dyes in artificially infected animals. With the aid of Mietzsch and Klarer a new compound was made from the original prontosil by adding an azonaphthalene ring to the sulfonamide group. This compound, disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′,6′-disulfonate, was the red dye which has been known and used as prontosil soluble and as prontosil and now is to be called neoprontosil. Domagk's work with the original prontosil in mice gave the impetus to the tremendous strides now being made in chemotherapy. To Domagk rightfully belongs the the credit for demonstrating the highly therapeutic activity of prontosil in artificially infected animals.

The investigations of Fourneau and co-workers,[5] Buttle, Gray and Stephenson,[6] Fuller[7] and Long and Bliss[8] led to the conclusion that the paraminobenzenesulfonamide group (sulfanilamide) is responsible for the therapeutic action of the prontosils and that the azo dye is not an essential component. The paraaminobenzenesulfonamide (sulfanil-

2. Eisenberg, P.: Untersuchungen über halbspezifische Desinfektionsvorgänge: I. Ueber die Wirkung von Farbstoffen auf Bakterien; Vitalfärbung-Entwickelungshemmung, Centralbl. f. Bakt. (Abt. 1) **71**:420, 1913.

3. Mietzsch and Klarer, cited by Hoerlein, H.: New Class of Chemotherapeutic Agents Against Streptococci, with Special Reference to Prontosil and Prontylin, M. Rec. **146**:11, 1937.

4. Domagk, G.: Ein Beitrag zur Chemotherapie der bakteriellen Infektionen, Deutsche med. Wchnschr. **61**:250, 1935.

5. Fourneau, E.; Tréfouël, J.; Tréfouël; Nitti, F., and Bovet, D.: Chimiothérapie des infections streptococciques par les dérivés du p-aminophénylsulfamide, Compt. rend. Soc. de biol. **122**:258, 1936.

6. Buttle, G. A. H.; Gray, W. H., and Stephenson, D.: Protection of Mice Against Streptococcal and Other Infections by *p*-Aminobenzenesulphonamide and Related Substances, Lancet **1**:1286, 1936.

7. Fuller, A. T.: Is *p*-Aminobenzenesulphonamide the Active Agent in Prontosil Therapy? Lancet **1**:194, 1937.

8. Long, P. H., and Bliss, E. A.: (*a*) Para-Amino-Benzene-Sulfonamide and Its Derivatives: Experimental and Clinical Observations on Their Use in the Treatment of Beta-Hemolytic Streptococcic Infection; Preliminary Report, J. A. M. A. **108**:32 (Jan. 2) 1937; (*b*) Use of Para Amino Benzene Sulphonamide (Sulphanilamide) or Its Derivatives in the Treatment of Infections Due to Beta Hemolytic Streptococci, Pneumococci and Meningococci, South. M. J. **30**:479, 1937.

amide) is set free by the reduction of the prontosils in the body. In vitro also the prontosils must be reduced before they become bacteriostatic.

Since the advent of sulfanilamide and the prontosils numerous derivatives have been introduced and tried both clinically and experimentally. Most of these are still in the experimental stage. Some have already shown great promise and against certain diseases appear to surpass both sulfanilamide and neoprontosil in effectiveness. The confusion arising from the various trade names of these derivatives is discouraging. The preparations encountered in this review of the literature are listed in the section headed "Definition of Terms."

DEFINITION OF TERMS

The original prontosil is the hydrochloride of 4-sulfamido-2',4'-diaminoazobenzene. It has been known by the following names:

Prontosil	D 5214
Prontosil flavum	Preparation 5214
Prontosil tablets	Rubiazol
Prontosil vulvum	Sulfamidochrysoidine
Red prontosil	

The term neoprontosil has recently been accepted by the Council on Pharmacy and Chemistry of the American Medical Association to designate disodium 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxy-naphthalene-3',6'-disulfonate. This compound has been known as prontosil soluble and as prontosil and has been designated also by the following names:

Prontosil	Prontosil solution
Prontosil soluble	Streptozon
Prontosil S	Streptozon S

The term sulfanilamide has been adopted bythe Council on Pharmacy and Chemistry of the American Medical Association to designate para-aminobenzenesulfonamide. The following additional names have been used:

Prontosil album	Stramid
Prontylin	Streptocide
Colsulanyde	Sulfamidyl
Deseptyl	Sulphonamide (or sulfonamide) P
1162 F	

In this review "sulfanilamide" is used to designate paraaminobenzene-sulfonamide. This term has been substituted for various trade names and synonyms encountered in the literature.

"The original prontosil" is used to designate the hydrochloride of 4-sulfamido-2',4'-diaminoazobenzene, and "neoprontosil" is used to designate disodium 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxy-

naphthalene-3′-6′-disulfonate in a 2.5 per cent solution. In instances in which another name was employed by an author whose work is cited, that designation is used in the text, and "the original prontosil" or "neoprontosil" is inserted in parentheses for identification. "The prontosils" is used to designate both the preparations just mentioned.

When other derivatives of sulfanilamide are mentioned, the designation employed by the original author is used in the text and if a more accurate or a more generally known descriptive term is available it is supplied in parentheses. Long chemical names are supplied in parentheses in only a few instances; the chemical names of all the preparations, however, are given in the following list of the derivatives of sulfanilamide mentioned in this review.

Derivatives of Sulfanilamide and Related Compounds Mentioned in This Review

Compound	Identification	Chemical Name
Dagenan	A brand of sulfapyridine *	
Dimethyldisulfanilamide		Paraaminobenzenesulfonylparaaminobenzenedimethylsulfonamide
Diseptal	A brand of dimethyldisulfanilamide	
Disulfanilamide	Same as sulfanilylsulfanilamide	
Disulon	A brand of sulfanilylsulfanilamide	
D 373	A brand of dimethyldisulfanilamide	
M & B 693	A brand of sulfapyridine *	
Proseptasine		Parabenzylaminobenzenesulfonamide
Sodium sulfanilylsulfanilate		N′-(phenyl-4-sodium sulfonate)-paraaminobenzenesulfonamide
Soluseptasine		Disodium p-(γ-phenylpropylamino)-benzenesulfonamide-α-γ-disulfonate
Sulfapyridine *		2-(paraaminobenzenesulfonamido)-pyridine
Sulfanilylsulfanilamide		Paraaminobenzenesulfonylparaaminobenzenesulfonamide
Uliron (Uleron)	A brand of dimethyldisulfanilamide	4,4′-di-(acetylamino)-diphenylsulfone 4,4′-diaminobenzenesulfonamide

*Name adopted by the Council on Pharmacy and Chemistry of the American Medical Association.

SULFANILAMIDE

This compound, which is the most widely used, is an almost odorless white crystalline powder, bitter with a slightly sweet after-taste. It is an aniline derivative, the amide of sulfanilic acid, and it contains 18.5 per cent sulfur. The American Medical Association through the Council on Pharmacy and Chemistry has examined twenty different American brands of sulfanilamide and found them all acceptable. It is slightly soluble (approximately 1 per cent) in hot water as well as in cold acetone and hot alcohol. It is insoluble in ether, chloroform and benzene. It is neutral to litmus in an aqueous solution.

Dosage.—Sulfanilamide is marketed in 5 and 7½ grain (0.32 and 0.48 Gm.) tablets, for oral administration, and also as a crystalline powder. As is the case with most drugs, infants and children tolerate sulfanilamide well in optimal doses. It can be given orally, subcutaneously, intramuscularly, intravenously or intrathecally, alone or by any combination of these routes. If oral and parenteral administration are combined, the twenty-four hour total dose is divided accordingly.

Oral Administration: Because sulfanilamide is well tolerated when given by mouth and absorption is complete and rapid, this is the method of choice when vomiting is not present. If the drug can be given by mouth and is tolerated, the same therapeutic effects will be obtained as with the other methods of administration, except possibly in the case of meningitis (see the section on meningitis). Parenteral administration may be the method of choice if extremely rapid, high concentration in the blood stream is desired or if sufficient concentration in the blood stream cannot be obtained because of decreased gastrointestinal absorption. This is not common. The majority of opinions favor oral administration when it is feasible.

The usual dose is 15 grains (0.97 Gm.) per 20 pounds (9.1 Kg.) of body weight per twenty-four hours, or 0.75 grain (0.049 Gm.) per pound up to 100 to 120 pounds (45.4 to 54.4 Kg.) For a person weighing more than this the dose should be reduced by one fourth. The dose is best divided equally during the twenty-four hours on a four or six hour schedule. Often on the first day half of the total amount is given as an initial dose, and the rest is then divided over the remaining part of the twenty-four hour period. This dosage will usually produce a concentration in the blood of about 10 mg. per hundred cubic centimeters. If expected therapeutic results are not being obtained, it is advisable to determine the concentration of sulfanilamide in the blood and if it is low to increase the dose of the drug until the desired concentration is obtained. This increase in dose is sometimes necessary because certain persons may show variation in the gastrointestinal absorption of the drug. In less severe infections a lower concentration in the blood

stream with decreased doses seems to be satisfactory, but in the more severe or critical infections larger doses with a concentration of 10 to 15 mg. per hundred cubic centimeters of blood may be necessary. As the infection subsides the dose can be decreased slowly, but it should be continued at a lower level for at least several days after the subsidence of severe infections. Withdrawal of the drug too soon often leads to recurrence of the infection.

For reasons not as yet clear a given dosage will not produce an equally high concentration of the drug in the blood stream in all persons, nor do similar infections in different persons respond equally well to the same levels of concentration in the blood stream. In other words, one sees apparently similar infections respond well to a concentration of 5 mg. per hundred cubic centimeters of blood, with a given dosage, in one child and in another child only to a concentration of 10 mg. or more, with the same dosage or a higher dosage.

Some have advocated giving an alkali, such as sodium bicarbonate, grain for grain with the sulfanilamide to combat possible acidosis. Hartmann, Perley and Barnett [9] suggested giving every four hours 1 to 2 cc. per kilogram of body weight of a half and half solution of sixth-molar sodium lactate and Ringer's solution (lactate-Ringer solution) instead of sodium bicarbonate because their investigations indicated a carbon dioxide deficit type of alkalosis rather than an alkaline deficit type of acidosis.

Subcutaneous and Intravenous Administration: For making solutions sulfanilamide in the form of crystalline powder should be used and not the tablets, as the latter contain a filler which is not soluble. Sulfanilamide is approximately 1 per cent soluble. A suitable solution for subcutaneous, intramuscular, intravenous or intrathecal administration is made by taking 100 cc. of a physiologic solution of sodium chloride or sixth-molar sodium lactate solution and bringing it to a boil, then adding 1 Gm. of the crystalline powder and allowing the solution to cool to body temperature before use. If too much sulfanilamide is used it will crystallize out. Hamilton [10] advocated using 10 cc. of sixth-molar sodium lactate solution per hundred cubic centimeters of the 1 per cent solution. He also stated that the solution, after it is made and sealed aseptically, can be stored in a refrigerator for two months and still safely be used. If any crystallization occurs, it will disappear on heating. The solution can also be sterilized by being boiled for ten minutes.

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9. Hartmann, A. F.; Perley, A. M., and Barnett, H. L.: Study of Some of the Physiological Effects of Sulfanilamide: Changes in the Acid-Base Balance, J. Clin. Investigation **17**:465, 1938.

10. American Academy of Pediatrics: Round Table Discussion on Sulfanilamide, J. Pediat. **13**:605, 1938.

The dose for the 1 per cent solution is 100 cc. per 40 pounds (18.1 Kg.) of body weight given every eight to twelve hours. It can be combined with oral and intraspinal therapy.

Intrathecal Administration: The solution just described can safely be given intraspinally and causes no irritation to the central nervous system. The amount is 5 to 10 cc. less than the amount of spinal fluid withdrawn, and administration can be repeated more than once daily, as indicated.

Local Application: Sulfanilamide and its derivatives have been applied locally to some extent. The use of the drug in dentistry has been associated with fairly dramatic results according to Sinclair,[11] who applied powdered sulfanilamide to infected tooth sockets after dental surgical procedures. He reported good results also in the case of compound fracture of the mandible with osteomyelitis. He observed no beneficial results from the local use of sulfanilamide against Vincent's infection. Bosse [12] reported favorable results when sulfanilamide, prontosil flavum (the original prontosil) and prontosil soluble (neoprontosil) were administered by direct application and spraying and inhalation in cases of erysipelas and bronchiectasis, respectively. Chandler [13] observed some beneficial results from powdered sulfanilamide applied locally to the chronic suppurating wounds of osteomyelitis.

Absorption and Excretion.—Absorption of sulfanilamide from the gastrointestinal tract is rapid; it has been found to be almost complete in four hours. Marshall, Emerson and Cutting [14] found that when sulfanilamide is given to human beings part of it is detoxified and conjugated in the organism and converted into paraacetylaminobenzenesulfonamide. Both free and conjugated forms are present in the blood stream and are excreted in the urine, etc.

The sulfanilamide becomes almost equally distributed in all the tissues of the body, with the exception of bone and fat. Its lower concentration in bone and fat is undoubtedly due to the decreased units of water in these tissues. Taking these facts into consideration, one can understand why sulfanilamide may seem less effective against certain infections. Because of the lower water content and the decreased blood

11. Sinclair, J. A.: Local Use of Sulfanilamide in the Treatment of Oral Lesions, J. Canad. Dent. A. **3**:571, 1937.

12. Bosse, G.: Ueber die Möglichkeit der örtlichen Prontosilanwendung in der inneren Klinik, Deutsche med. Wchnschr. **64**:116, 1938.

13. Chandler, F.: Personal communication to the authors.

14. Marshall, E. K., Jr.; Emerson, K., Jr., and Cutting, W. C.: Para-Aminobenzenesulfonamide; Absorption and Excretion: Method of Determination in Urine and Blood, J. A. M. A. **108**:953 (March 20) 1937. Marshall, E. K., Jr.; Cutting, W. C., and Emerson, K., Jr.: Acetylation of Para-Aminobenzenesulfonamide in Animal Organism, Science **85**:202, 1937.

supply, infections of bone and fat, encapsulated abscesses and infections with surrounding fibrosis or sclerosis cannot receive sufficient sulfanilamide for efficient rapid action.

Excretion in Urine: About 93 per cent (Stewart and associates [15]) of the sulfanilamide taken into the body is excreted in the urine in the free and conjugated forms. According to Marshall, Emerson and Cutting,[14] when large amounts of sulfanilamide are given nearly 100 per cent as free and conjugated forms are recovered from the urine. Equilibrium between intake and urinary output is reached in two or three days. It takes only two or three days for all the drug to be eliminated from the body after administration has been stopped. It does not accumulate in the tissues. When renal excretion is impaired, excretion takes place more slowly. When diuresis is present, excretion is more rapid. The concentration of sulfanilamide in the urine is about ten times greater than that in the blood (usually 100 to 500 mg. per hundred cubic centimeters of urine), and for this reason the urine can more easily be made highly bactericidal.

Excretion in Breast Milk: Sulfanilamide is also excreted in both conjugated and free forms in breast milk. Adair and Hesseltine [16] found that about 1.5 per cent of the drug given to a lactating mother is excreted in the breast milk. Stewart and co-workers [15] showed that the concentration of free sulfanilamide in the breast milk usually runs about parallel to that in the blood. When oral administration of the drug is discontinued, the concentration in the breast milk rapidly falls. Babies fed entirely by breast showed no clinical evidence of toxic manifestations when sulfanilamide was present in the milk in a concentration of 7 mg. per hundred cubic centimeters. This corresponds to a dose of about 28 mg., or ½ grain, per twenty-four hours for the baby. The urine of such infants contains from 1 to 2.6 mg. of sulfanilamide per hundred cubic centimeters during twenty-four hours, and traces are present in the blood.

Excretion in Amniotic Fluid and Other Fluids: Sulfanilamide passes into the amniotic fluid in a concentration equal to that in the maternal blood. The drug is also excreted in small amounts in the cervical secretion and in the menstrual flow.

Concentration in the Blood Stream.—Sulfanilamide because of its rapidity of absorption passes into the blood stream rapidly and in high

15. Stewart, H. L., Jr., and Pratt, J. P.: Sulfanilamide Excretion in Human Breast Milk and the Effect on Breast-Fed Babies, J. A. M. A. **111**:1456 (Oct. 15) 1938. Stewart, J. D.; Rourke, G. M., and Allen, J. G.: Excretion of Sulfanilamide, ibid. **110**:1885 (June 4) 1938.

16. Adair, F.; Hesseltine, H., and Hac, L. R.: An Experimental Study of the Behavior of Sulfanilamide, J. A. M. A. **111**:766 (Aug. 27) 1938.

concentrations. It is generally conceded that a concentration of 10 mg. per hundred cubic centimeters of blood is sufficient for most infections. Concentrations as high as 40 mg. per hundred cubic centimeters have been reached with no deleterious effects. Both the conjugated and the free form of sulfanilamide are found in the blood in about the following relationship: Of a total of 16 mg. per hundred cubic centimeters of blood, 14 mg. is in the free and 2 mg. in the conjugated, or aceytlated, form. Frequent determinations of concentration are necessary if one is to give intelligently the optimal dose of the drug.

From the maternal blood stream sulfanilamide passes through the placenta into the fetal circulation, so that in from three to five hours the concentration of the free and of the conjugated form is about equal in both maternal and fetal blood. As yet it has not been shown that this has any harmful effect on the fetus.

Concentration in the Spinal Fluid.—The drug appears in the spinal fluid and in the blood stream almost simultaneously and the concentration in the spinal fluid is about three fourths that in the blood. It is secreted into the spinal fluid just as rapidly and in as high concentration when given orally as when administered parenterally. It causes no irritation of the central nervous system, even when a solution is injected intraspinally.

NEOPRONTOSIL

Neoprontosil is soluble in cold water and when dissolved forms a red liquid. It can be administered intramuscularly, intrathecally or intravenously. It is now marketed in 2.5 per cent and in 5 per cent solution and in tablet form (5 grains) for oral administration. The dose recommended for intravenous and intramuscular administration is 1 cc. of the 2.5 per cent solution per pound (0.45 Kg.) of body weight and 0.75 cc. per pound for persons over 120 pounds (54.4 Kg.) in weight. It has been estimated that about 100 cc. of the 2.5 per cent solution is equivalent to 0.75 Gm. of sulfanilamide. This active principle is released by reduction in the body. Neoprontosil stains the urine and tissue red within fifteen minutes after it is administered. The dye itself does not pass into the spinal fluid from the blood stream, but the available free sulfanilamide does. Neoprontosil and sulfanilamide can be administered at the same time. It is questionable at the present time whether the chemotherapeutic effect of neoprontosil is entirely due to the available sulfanilamide it contains. Neoprontosil at times has a therapeutic effect equivalent to that of a much larger dose of sulfanilamide than is available in this preparation. This increased therapeutic action then must be due to something in the compound other than the paraaminobenzenesulfonamide (sulfanilamide).

MODE OF ACTION

Various theories have been advanced as to the mode of action of sulfanilamide, but none is entirely adequate. Bliss and Long [17] stated the belief that the action is one of bacteriostasis. The drug itself is not strongly bactericidal; so it seems probable that the destruction of the bacteria is accomplished by the defense mechanisms of the body, which are aided in some way by the drug. In vitro the rate of bacterial cell division seems to be decreased. Osgood [18] expressed the opinion that in some way there is neutralization of bacterial toxins, which makes the organisms more susceptible to the defense mechanisms of the body. This has not been found true by other workers. Meyer [19] stated the belief that sulfanilamide inhibits the formation of toxin in the organisms but does not neutralize the toxin already present. The drug does not act through the leukocytes by increasing their number or by changing the polymorphonuclear-lymphocyte ratio, as shown by Bigler, Clifton and Werner.[20] Campbell [21] expressed the idea that it may produce a mild stimulus of the bone marrow, with a slight increase in the circulating reticulocytes. Coman [22] claimed that the therapeutic effect is not due to chemotropism of the leukocytes. It is possible that the capsule of the organism is so changed by absorption of the drug that injury results. At the site of the infection there are no demonstrable local histologic changes which can be ascribed to sulfanilamide therapy. Except in undulant fever there is no evidence of increased phagocytosis. It appears that the drug enhances the bactericidal properties of human serum and leukocytes so that they destroy bacteria they would otherwise not be able to affect.

TOXICITY

Sulfanilamide produces no signs of chronic toxicity, nor does it produce any pathologic lesions. Animals given lethal doses have symptoms of vestibular dysfunction, convulsions and spastic paralysis, indi-

17. Bliss, E. A., and Long, P. H.: Observations on the Mode of Action of Sulfanilamide, J. A. M. A. **109**:1524 (Nov. 6) 1937.

18. Osgood, E. E.: Culture of Human Marrow: Studies on the Mode of Action of Sulfanilamide, J. A. M. A. **110**:349 (Jan. 29) 1938.

19. Meyer, F.: The Mechanism of the New Chemotherapy, Brit. M. J. **1**: 810, 1938.

20. Bigler, J. A.; Clifton, W. M., and Werner, M.: Leukocyte Response to Sulfanilamide Therapy, J. A. M. A. **110**:343 (Jan. 29) 1938. Bigler, J. A.: Blood Cell Response to Sulfanilamide Therapy, Ann. Otol., Rhin. & Laryng. **47**:219, 1938.

21. Campbell, C. M., Jr.: Effect of Sulphanilamide on the Blood Picture, Lancet **1**:247, 1938.

22. Coman, D. R.: Effect of Prontosil and Related Compounds upon the Chemotropism of Leukocytes, Am. J. M. Sc. **195**:574, 1938; **196**:273, 1938.

cating that the central nervous system is most affected.[23] These symptoms have never been reported to occur in human beings.

The toxic symptoms occurring during administration of sulfanilamide can be placed in several groups, according to their nature and severity. The more severe will be taken up in detail.

Allergic Symptoms.—Typical allergic responses seem to be rare. Salvin [24] reported these symptoms in a 22 year old patient. Sulfanilamide therapy was started, 10 grains (0.65 Gm.) being given four times a day. The next day there was intense itching of the skin, with urticaria, swelling and edema of the eyelids, lips and scrotum, sneezing, lacrimation and shortness of breath. Epinephrine was given, and by the following day the symptoms had completely disappeared. A patch test with sulfanilamide elicited a positive reaction. When 1 grain (0.06 Gm.) of the drug was again given by mouth, itching of the skin and sneezing recurred within twelve hours. A case of similar allergic symptoms was reported by Schonberg.[25] Urticaria-like lesions are often part of a sulfanilamide rash.

Mild Toxic Symptoms.—These occur frequently, usually from twenty-four to seventy-two hours after medication is started. They consist of nausea, vomiting, abdominal pain, diarrhea, increased urination, anorexia, malaise and weakness, dizziness, vertigo, tinnitus, tingling sensations, mild psychosis or disorientation, fever, rash, acidosis and cyanosis. These symptoms always disappear promptly on withdrawal of the drug, and frequently they disappear if the drug is continued. However, if the drug is continued, the patient should be closely observed.

Severe Toxic Symptoms.—These are seldom seen. They include hyperpyrexia, rash, shock, jaundice, sulfhemoglobinemia, methemoglobinemia, anemia, leukopenia and agranulocytosis, optic neuritis, peripheral neuritis and psychosis.

Toxic Reactions Involving the Blood.—By far the most serious toxic reactions attributed to sulfanilamide involve the blood cells. Unfortunately the patch, scratch or intradermal cutaneous tests for sensitivity to drugs are of little value in cases of hematologic sensitivity. Sensitization to a certain drug, once acquired, seems to be more or less permanent.[26] This does not seem to apply to the cyanosis so frequently seen during sulfanilamide therapy, as will be discussed later.

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23. Hageman, P. O.: Toxicity of Sulfanilamide, Proc. Soc. Exper. Biol. & Med. **37**:119, 1937. Hawking, F.: Pharmacological Actions of Sulphanilamide, Lancet **2**:1019, 1937.

24. Salvin, M.: Hypersensitivity to Sulfanilamide, J. A. M. A. **109**:1038 (Sept. 25) 1937.

25. Schonberg, I. L.: Purpuric and Scarlatiniform Eruption Following Sulfanilamide, J. A. M. A. **109**:1035 (Sept. 25) 1937.

26. Fitz-Hugh, T.: Sensitivity Reaction of the Blood and Bone Marrow to Certain Drugs, J. A. M. A. **111**:1643 (Oct. 29) 1938.

1. Agranulocytosis and Leukopenia: When daily determinations of blood cells were made for children receiving sulfanilamide, Bigler and his co-workers [20] found that there was a definite tendency toward the development of leukopenia without neutropenia. If the leukocyte count decreases to 5,000 or less or if beginning neutropenia becomes evident, extreme care should be exercised in continuing administration of the drug. When large doses are being used or when medication is to be continued for several days, it is advisable to have frequent blood counts made. Kracke,[27] in recently reviewing the literature on neutropenia due to drug therapy, found 11 cases in which the condition was attributed to sulfanilamide. In these there were 9 deaths and 2 recoveries. Of the patients 1 was an infant, 2 were older children and the others were mostly young adults. In all cases large amounts of the drug were taken, the total dose being 40 to 50 Gm. for adults. The drug was given for eighteen days or longer except in the case of 1 of the children, to whom it was given for seven days only. The leukocyte count ranged from 400 to 1,800 and the proportion of neutrophils from 0 to 1 per cent. Of the 2 patients who recovered, 1 did so spontaneously and the other received pentnucleotide and liver extract. Although the occurrence of agranulocytosis is rare, it is a most serious complication. When it is present or impending, there should be prompt withdrawal of the drug, and blood transfusions, pentnucleotide and/or yellow bone marrow should be given.

2. Anemia: This condition, evidenced by a moderate drop, of about 10 per cent, in hemoglobin content and a moderate decrease in red blood cells, is frequently seen during sulfanilamide therapy and usually can be accounted for by the infection. If the anemia progresses or suddenly becomes more marked, the drug should be withdrawn and blood transfusions given. The usual type of anemia reported is hemolytic, sudden in onset and severe. Fortunately it responds well to withdrawal of the drug and blood transfusions. Harvey and Janeway [28] reported 3 cases of acute hemolytic anemia, during sulfanilamide therapy, 1 of the patients being a child 10 months of age. The onset occurred between the second and the seventh day of therapy. Jaundice was present in 2 of the patients. There was a rapid fall of the hemoglobin level to between 30 and 40 per cent, with a proportional decrease in the red cells, and in all 3 patients there was leukocytosis, the white cell count ranging from 30,000 to 87,000. All patients recovered with blood transfusions.

27. Kracke, R. R.: Relation of Drug Therapy to Neutropenic States, J. A. M. A. **111**:1255 (Oct. 1) 1938.

28. Harvey, A. M., and Janeway, C. A.: Development of Acute Hemolytic Anemia During the Administration of Sulfanilamide, J. A. M. A. **109**:12 (July 3) 1937.

Kohn [29] reported a case of hemolytic anemia in a 1 year old infant after twelve doses of sulfanilamide of 5 grains (0.32 Gm.) each. There were jaundice and a fall of the hemoglobin level to 6 Gm. and of the red cell count to 2,000,000. Rapid improvement occurred after a blood transfusion. The Rosenblums [30] reported a case of severe hemolytic anemia with recovery in a 10 year old child. We have observed a similar case. Greenthal [31] reported that acute hemolytic anemia developed in a 23 month old child during hemolytic streptococcic sepsis before sulfanilamide was administered. In spite of this 60 grains (3.88 Gm.) of the drug was given over a four day period, and the patient promptly recovered from the infection. However, one month was required to correct the anemia, in spite of blood transfusions. W. B. Wood [32] reported that acute anemia developed in 21, or 4 per cent, of 522 patients receiving sulfanilamide. All patients recovered on withdrawal of the drug and, in case of severe involvement, the giving of blood transfusions. The incidence of this complication seems to be higher in children (12, or 8.3 per cent, of 144 treated) than in adults. The onset always occurred between the third and the seventh day of therapy. There was no relation between the type of infection or the dose of sulfanilamide and the occurrence of the anemia. In all cases it occurred in patients with a temperature over 102 F. In the patients with anemia the highest concentration of the drug in the blood was 10.7 mg. per hundred cubic centimeters, as compared with 40 mg. in some patients who did not have anemia. There was a rapid fall of 25 to 71 per cent in hemoglobin level, with marked decrease in red blood cells. Wood listed the following aids to early diagnosis: (1) nausea and dizziness twelve to twenty-four hours before onset of anemia; (2) increased secretion of urobilin in the urine; (3) unexplained elevation of temperature from the third to the fifth day of therapy; (4) sudden fall in hemoglobin content twenty-four to seventy-two hours after the start of therapy, and (5) hyperbilirubinemia and jaundice. He stated that the drug should not be given to patients who have recovered from acute anemia, because in 4 of 5 of his patients there was recurrence of the anemia when the drug was given again. H. Wood [33] reported a death from acute hemolytic anemia which

29. Kohn, S. E.: Acute Hemolytic Anemia During Treatment with Sulfanilamide, J. A. M. A. **109**:1005 (Sept. 25) 1937.

30. Rosenblum, P., and Rosenblum, A.: Severe Hemolytic Anemia Due to Sulfanilamide, Arch. Pediat. **55**:511, 1938.

31. Greenthal, R. M.: Acute Hemolytic Anemia Developing During Streptococcic Sepsis, J. Pediat. **12**:517, 1938.

32. Wood, W. B., Jr.: Anemia During Sulfanilamide Therapy, J. A. M. A. **111**:1916 (Nov. 19) 1938.

33. Wood, H.: Fatality from Acute Hemolytic Anemia Which Developed During the Administration of Sulfanilamide, South. M. J. **31**:646, 1938.

occurred during sulfanilamide therapy. Although the acute anemia is serious, the prognosis is good with prompt withdrawal of the drug and with the use of blood transfusions.

3. Leukemoid Reactions: It has been observed [34] occasionally that marked leukocytosis, with 30,000 to 90,000 white cells, may occur. Such reactions have often been accompanied by other toxic symptoms. With this increase in leukocytes there usually is a shift to the left, with the appearance of early cell forms. As yet no serious results have been reported in such cases. The leukocyte count returns to normal on withdrawal of the drug.

4. Cyanosis: This is one of the most common complications occurring during sulfanilamide and neoprontosil therapy. It has been observed to some degree in at least half of the patients receiving the drug. Its occurrence does not seem to depend on the age of the patient, the daily dose or the length of time of administration. It may occur in patients with or without infections. When cyanosis is present, the patient rarely experiences any discomfort, and the respirations are not accelerated. It is first noticed and becomes most prominent about the lips and the finger nails. The cyanosis usually occurs early, most often from the second to the fourth day after therapy is started. The blood becomes darker than normal. This change is commensurate with the degree of cyanosis, the blood even becoming dark brown. On coagulation of the blood the serum is found to have a normal color. The change, then, occurs in the solid elements, most likely being due to some pigment change in the red blood cells. When determinations of hemoglobin are made by the Sahli method the readings may be high.

At first there was great concern over the presence of cyanosis because of its possible relation to sulfhemoglobinemia and methemoglobinemia. In most of the cases reported early in the English literature [35] sulfhemoglobin or methemoglobin bands were found spectroscopically when the blood was examined. Such bands were often present even before the appearance of cyanosis. In many of the cases of English authors sulfur in the form of magnesium sulfate had been given with the drug. Accord-

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34. Myers, G. B.; Vonder Heide, E. D., and Balcerski, M.: Exfoliative Dermatitis Following Sulfanilamide, J. A. M. A. **109**:1983 (Dec. 11) 1937. Kracke.[27] Harvey and Janeway.[28]

35. (*a*) Archer, H. E., and Discombe, G.: Sulphaemoglobinaemia: Its Cause and Prevention, with Special Reference to Treatment with Sulphanilamide, Lancet **2**:432, 1937. (*b*) Paton, J. P. J., and Eaton, J. C.: Sulphaemoglobinaemia and Methaemoglobinaemia Following Administration of *p*-Aminobenzenesulphonamide, ibid. **1**:1159, 1937. (*c*) Colebrook, L., and Kenney, M.: Treatment of Human Puerperal Infections, and of Experimental Infections in Mice, with Prontosil, ibid. **1**:1279, 1936. (*d*) Frost, L. D. B.: Sulphaemoglobinaemia Following Antistreptococcal Chemotherapy, ibid. **1**:510, 1937.

ing to most of the reports dealing with cyanosis in this country, sulfhemoglobin and methemoglobin bands have not been demonstrable spectroscopically. Marshall and Walzl [36] studied 7 cases of cyanosis occurring during sulfanilamide medication. In only 1 of the 3 cases in which examination was made were absorption bands of methemoglobin present. In only 2 of the cases was there any inactive hemoglobin, and it was present in only small amounts. They concluded that cyanosis may not be due to nonfunctional iron pigment. Bigler and Werner [37] studied the blood of cyanotic patients; in none could methemoglobin or sulfhemoglobin absorption bands be demonstrated. Cyanosis occurred when no inactive hemoglobin was present as well as when there were large amounts, and in 1 case there was no cyanosis, although 25 per cent of the hemoglobin was inactive. In 8 cyanotic patients observed by Chesley [38] methemoglobin and sulfhemoglobin were absent or present in negligible amounts. Ottenberg and Fox [39] exposed dilute solutions of sulfanilamide to ultraviolet radiation and a strong violet color developed in the solutions. When erythrocytes were added to such solutions they assumed the color of erythrocytes of patients under sulfanilamide therapy. They stated the opinion that the cyanosis may have been due to metabolic transformation of the drug in vivo to a colored compound.

The cyanosis usually persists for only a few days after withdrawal of the drug and often does not reappear when the drug is administered again. It is not affected by the giving of oxygen but is lessened when blood transfusions are given. Wendel [40] advocated the intravenous administration of methylene blue (methylthionine chloride) in doses of 1 mg. per kilogram of body weight. It will cause rapid disappearance of the cyanosis. Only 1 fatal case has been reported in which cyanosis was present and in which spectroscopic examination of the blood post mortem revealed the presence of sulfhemoglobinemia. This, reported by Frost,[35d] was the case of a 12 year old girl with an infection of the knee due to an injury. She received 10 cc. of prontosil (neoprontosil) and 12 tablets of proseptasine (parabenzylaminobenzenesulfonamide) over two days, at which time the temperature became normal and remained so. Cyanosis began on the second day of medication, and death occurred

36. Marshall, E. K., and Walzl, E. M.: Cyanosis from Sulfanilamide, Bull. Johns Hopkins Hosp. **61**:140, 1937.

37. Bigler, J. A., and Werner, M.: Cyanosis from Sulfanilamide, Am. J. Dis. Child., to be published.

38. Chesley, L. C.: Cyanosis Without Sulf- or Methemoglobinemia in Patients Receiving Sulfanilamide Treatment, J. Clin. Investigation **17**:445, 1938.

39. Ottenberg, R., and Fox, C. L.: Explanation for Cyanosis of Sulfanilamide Therapy, Proc. Soc. Exper. Biol. & Med. **38**:479, 1938.

40. Wendel, W. B.: Use of Methylene Blue in Methemoglobinemia from Sulfanilamide Poisoning, J. A. M. A. **109**:1216 (Oct. 9) 1937.

two days later. The postmortem diagnosis was marked early hypostasis, streptococcic pus in the knee, early fatty change of the liver, darkness and fluidity of the blood and sulfhemoglobinemia.

It has been found that when cyanosis due to sulfhemoglobinemia or methemoglobinemia results from other drug therapy, if caused by the former it usually lasts for several weeks, while if due to the latter it usually lasts only twenty-four to forty-eight hours.

As yet it is not known just what causes the cyanosis which occurs during medication with sulfanilamide and neoprontosil. Certainly in the majority of cases it is not due to sulfhemoglobin and possibly not to methemoglobin. Some other pigment may be responsible. The oxygen saturation of the arterial blood is not decreased sufficiently to produce the cyanosis.[41] In our experience cyanosis has not been an alarming symptom, and we have not hesitated to continue giving the drug, if necessary, even when cyanosis was present. Usually the cyanosis disappeared just as quickly while the medication was being continued as when it was stopped. In 1 extremely ill patient with hemolytic streptococcic meningitis and mastoiditis cyanosis developed on the second day of sulfanilamide therapy. On that and the next day the blood contained 45 to 50 per cent inactive hemoglobin. The drug was continued in one third the previous dosage for three more weeks, and the cyanosis disappeared spontaneously by the sixth day and did not recur. The patient recovered. However, when cyanosis is present the patient should be carefully observed.

5. Rash: Although this toxic manifestation of sulfanilamide and neoprontosil therapy occurs in about 6 per cent of the patients, it is relatively uncommon in children. The rash is commonly a red to brown maculopapular morbilliform eruption most frequently involving the face, neck, arms, hands, buttocks, legs and feet and less often the shoulders and trunk. There may be erythema with urticaria-like lesions, and purpuric lesions may be present. The rash usually occurs after three to fourteen days of medication. Fever, often with a temperature as high as 104 F., may be present, as well as itching, edema and swelling of the skin. The eruption has been found to be most pronounced over areas exposed to the sun. The rash may last two to six days; it disappears spontaneously on withdrawal of the sulfanilamide or even while it is still being given. It is seen most frequently in ambulatory patients. Schwentker and Gelman [42] found a morbilliform rash in 6 per cent of their series of 180 patients treated orally and parenterally with sulf-

41. King, F. H.; Leslie, A., and Byrne, G.: Oxygen Saturation of Arterial Blood in Cyanosis from Sulfanilamide, J. A. M. A. **110**:2069 (June 18) 1938.

42. Schwentker, F. F., and Gelman, S.: Sulfanilamide Rash, Bull. Johns Hopkins Hosp. **61**:136, 1937.

anilamide. This rash appeared between the third and the seventeenth day of the drug therapy and was accompanied by a temperature of 101 to 103 F. The rash usually disappeared within forty-eight hours after the cessation of the sulfanilamide treatment and within seventy-two hours if this therapy was not discontinued. Of 134 patients given sulfanilamide by Hageman and Blake,[43] in 9 there developed a febrile reaction and an itching maculopapular, urticaria-like rash with hemorrhagic lesions. Erosions of the oral mucous membranes occurred in Noun's case.[44] Myers and co-workers [34] reported a case of exfoliative dermatitis in a 25 year old man who had had a total of 1,300 grains (84.24 Gm.) of sulfanilamide. There were swelling of the eyelids, a morbilliform rash, edema of the skin and desquamation over the entire body. Saphirstein [45] also reported a case in which erythema and desquamation occurred. In 1 case of rash reported by Myers and associates [34] the result of the patch test was positive, while in 1 case reported by Goodman and Levy [46] the result of the scratch test was suggestive and in 1 case results of the patch, scratch and intradermal tests for sulfanilamide were negative. Schonberg,[25] Goodman and Levy,[46] Newman and Sharlit,[47] Frank [48] and Schwentker and Gelman [42] have reported cases in which there was recurrence of the rash with itching of the skin when the drug was readministered. That the drug may produce photosensitiveness was demonstrated by Brunsting,[49] who found large amounts of prophyrin in human urine. Newman and Sharlit [47] found that on ultraviolet irradiation of the skin of a patient being treated with sulfanilamide the rash occurred over the treated areas.

6. Fever: Patients with a temperature as high as 106 F. after sulfanilamide therapy have been reported on. The fever usually lasts for from one to four days and is frequently accompanied by a rash. Long and Bliss [8a] reported febrile reactions in a normal human being

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43. Hageman, P. O., and Blake, F. G.: A Specific Febrile Reaction to Sulfanilamide: Drug Fever, J. A. M. A. **109**:642 (Aug. 28) 1937.

44. Noun, M. H.: Erosions of the Oral Mucosa and Urticaria of the Body Following Small Doses of Sulfanilamide, Arch. Dermat. & Syph. **37**:1044 (June) 1938.

45. Saphirstein, H.: Hepatitis and Toxic Erythema with Desquamation Due to Sulfanilamide, Urol. & Cutan. Rev. **42**:101, 1938.

46. Goodman, M. H., and Levy, C. S.: Development of a Cutaneous Eruption During Sulfanilamide Administration, J. A. M. A. **109**:1009 (Sept. 25) 1937.

47. Newman, B. A., and Sharlit, H.: Sulfanilamide: A Photosensitizing Agent of the Skin, J. A. M. A. **109**:1036 (Sept. 25) 1937.

48. Frank, L. J.: Dermatitis from Sulfanilamide, J. A. M. A. **109**:1011 (Sept. 25) 1937.

49. Brunsting, L. A.: Sulfanilamide Dermatitis, Proc. Staff Meet., Mayo Clin. **12**:614, 1937.

50. Footnote deleted.

after the injection of 100 cc. of prontosil solution (neoprontosil). Hageman and Blake [43] in a series of 134 patients treated with sulfanilamide found a specific febrile reaction in 21, or 15.6 per cent. The fever occurred as early as the fourth and as late as the thirteenth day and lasted from two to four days. It was abrupt in onset; often it was accompanied by malaise, nausea, itching or tinnitus, and in 9 cases it was associated with a rash.

One should suspect that a febrile reaction is due to the drugs and not to the infection if the onset is abrupt and unexplained and occurs after one or more days of a normal temperature and if it is not accompanied by symptoms of the original infection but by some other toxic manifestations, or if the patient does not appear clinically ill. Withdrawal of the drug is the only treatment needed to correct febrile reactions of sulfanilamide.

7. Acidosis: This has been reported to occur when large doses of sulfanilamide were given or when prolonged medication was necessary. No serious results have followed its occurrence. Its prevention and correction have been discussed under the heading "Dosage of Sulfanilamide."

8. Disorders of Nervous System: Wigton and Johnson [51] reported 4 cases of peripheral neuritis which followed the use of sulfanilylsulfanilamide, or disulfanilamide, in 3 cases and uliron (dimethyldisulfanilamide) in 1 case. Residual symptoms persisted many months, with only slight or no improvement after discontinuance of the drug. Tietze [52] reported 2 cases of complete paralysis of the legs and hands following the use of uliron (dimethyldisulfanilamide). Neither patient showed any tendency to improve, and 1 showed increasing atrophy. Gelbjerg-Hansen and Krabbe [53] reported 1 case of polyneuritis produced by uliron (dimethyldisulfanilamide). Bannick, Brown and Foster [54] reported the occurrence of peripheral neuritis in patients treated with dimethyldisulfanilamide. In Germany, where uliron (dimethyldisulfanilamide) is used a great deal, in a large number of cases peripheral neuritis has resulted. In most cases the paralysis did not improve over a period of months, even though vitamin B_1 was used extensively. The paralysis usually occurs in adults after about the third week of administration of from 2.5 to 5 Gm. a day.

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51. Wigton, R. S., and Johnson, S. H., III.: Peripheral Neuritis Following Sulfanilyl Sulfanilamide (Disulfanilamide): Report of Four Cases, J. A. M. A. **111**:1641 (Oct. 29) 1938.

52. Tietze, A.: Periphere Lähmungen nach Ulironbehandlung, München. med. Wchnschr. **85**:332, 1938.

53. Gelbjerg-Hansen, G., and Krabbe, K. H.: Polyneuritis Caused by Uliron, Ugesk. f. læger **100**:568, 1938.

54. Bannick, E. G.; Brown, A., and Foster, F.: Therapeutic Effectiveness and Toxicity of Sulfanilamide and Several Related Compounds, J. A. M. A. **111**: 770 (Aug. 27) 1938.

Hogan and McNamara [55] reported a case of psychosis precipitated by sulfanilamide. In this instance, 940 grains (60.91 Gm.) of the drug had been given in seventeen days and, after a five day rest, 240 grains (15.55 Gm.) in four days. The psychosis persisted for one month after withdrawal of the drug. Danziger [56] also reported a case of psychosis with marked negativism occurring after sulfanilamide therapy.

Bucy [57] reported a case of optic neuritis which occurred in a girl 16 years of age treated with 250 grains (16.2 Gm.) of sulfanilamide over eleven days for a pelvic abscess. The optic neuritis appeared on the eleventh day and cleared up within four days after withdrawal of the drug.

We have found in the literature no reports of peripheral neuritis or psychosis in children. So far only 1 case [58] of peripheral neuritis due to sulfanilamide has been reported. This occurred in a Negro aged 42 years, who in about five weeks took 130 Gm. (2,000 grains) of sulfanilamide. Residual findings were still present after three months.

CONTRAINDICATIONS TO THERAPY

The contraindications for the use of sulfanilamide compounds are as follows: a hemoglobin level as low as 30 per cent, severe renal damage, hepatic damage, jaundice, leukopenia, neutropenia or any previous untoward reaction to the drug, such as acute hemolytic anemia and allergic reactions. The use of sulfates and drugs of the aniline group in conjunction with sulfanilamide is contraindicated, in view of their tendency to cause sulfhemoglobinemia, methemoglobinemia and neutropenic states. Moreover, the drug should not be given to patients who cannot be kept under close observation. It should not be prescribed in forms or vehicles not investigated by the Council on Pharmacy and Chemistry of the American Medical Association.

There is no contraindication to using the ordinary narcotics, such as morphine and codeine, in conjunction with sulfanilamide. Other drugs in common use may also be given with sulfanilamide, if close observation of the patient is possible.

INFECTIONS AND DISEASES BENEFITED BY SULFANILAMIDE

1. *Streptococcic Infections.*—A. Beta Hemolytic Streptococcus: Hemolytic streptococcic infections in man belong primarily but not

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55. Hogan, G. W., and McNamara, P. J.: Psychosis Precipitated by Sulfanilamide, U. S. Nav. M. Bull. **36**:60, 1938.

56. Danziger, L.: Delayed Toxic Reaction to Sulfanilamide, Bull. Johns Hopkins Hosp. **63**:340 (Nov.) 1938.

57. Bucy, P.: Toxic Optic Neuritis Resulting from Sulfanilamide, J. A. M. A. **109**:1007 (Sept. 25) 1937.

58. Ornsteen, A. M., and Furst, W.: Peripheral Neuritis Due to Sulfanilamide, J. A. M. A. **111**:2103 (Dec. 3) 1938.

exclusively to the Lancefield group A. The minute hemolytic streptococci of Bliss,[59] classified by Lancefield in group F, are seen occasionally. The anaerobic hemolytic streptococci, according to Fisher,[60] are frequently found in abscesses of the lung and may cause puerperal sepsis. Bliss, Long and Feinstone [61] observed bacteriostatic effects in vitro with sulfanilamide on groups A, B and C but no effect on groups D and F.

(*a*) Erysipelas. The treatment of erysipelas prior to the advent of sulfanilamide was only fairly satisfactory. The use of various types of antistreptococcus serum or of ultraviolet radiation, roentgen therapy, blood transfusions and the like leaves much to be desired in the treatment of this disease in children. To our knowledge, no drug yet used has shown so remarkable a specific action against erysipelas as have neoprontosil and sulfanilamide. There are usually definite fading of the rash and cessation of its spread within twelve hours. Rotter [62] reported 100 cases of erysipelas treated successfully with prontosil tablets (the original prontosil) and prontosil solution (neoprontosil). Marzollo [63] in treating 26 patients with prontosil tablets (the original prontosil) given orally found that the fever subsided and the leukocyte count decreased during the first or second day of the treatment. Breen and Taylor [64] treated 33 patients with sulfanilamide and 2 with prontosil (neoprontosil) and noted regression of the disease within forty-eight hours. The average hospital stay in this group was eighteen and four-tenths days, in contrast to twenty-three and eight-tenths days for the control series. Snodgrass and Anderson [65] treated 135 patients with sulfanilamide and an equal number with ultraviolet radiation. Of the sulfanilamide-treated group, 96.9 per cent showed no further spread after twenty-four hours, in contrast to only 59 per cent in the control series. Of the sulfanilamide-treated series 75.2 per cent showed no fever after forty-eight hours, in contrast to 47.3 per cent of the controls. No toxemia after forty-eight hours was noted in 46.9 per cent of the

59. Bliss, E. A.: Studies upon Minute Hemolytic Streptococci: Serological Differentiation, J. Bact. **33**:625, 1937.

60. Fisher, A. M., and Abernethy, T. J.: Putrid Empyema, with Special Reference to Anaerobic Streptococci, Arch. Int. Med. **54**:552 (Oct.) 1934.

61. Bliss, E. A.; Long, P. H., and Feinstone, W. N.: The Differentiation of Streptococci and Its Relation to Sulfanilamide Therapy, South. M. J. **31**:303, 1938.

62. Rotter, H.: Zur Chemotherapie der Kokkenerkrankungen: Erfahrungen bei der Behandlung des Rotlaufes mit Prontosil, Dermat. Ztschr. **74**:325, 1937.

63. Marzollo: Contributo allo studio della teropia dell'eresipela con i composti azoici, Gior. veneto di sc. med. **11**:340, 1937.

64. Breen, C. E., and Taylor, I.: Erysipelas Treated with Prontosil, Lancet **1**:1334, 1937.

65. Snodgrass, W. R., and Anderson, T.: Sulphanilamide in the Treatment of Erysipelas: A Controlled Series of Two Hundred and Seventy Cases, Brit. M. J. **2**:1156, 1937.

sulfanilamide-treated group, in contrast to 37.7 per cent of the controls. We have treated in several young infants and children mild or severe erysipelas, with spectacular results. We have found it advisable to give the sulfanilamide in full dosage until the fever and toxemia have subsided and the rash has regressed. Then the dose should be gradually reduced, but the drug should be continued for several days after clinical improvement, in order to prevent recurrences of the disease. Neoprontosil can be used satisfactorily if oral medication is not feasible. At present it is felt that sulfanilamide is the treatment of choice.

(*b*) Otitis Media and Mastoiditis.[66] The criteria for the use of sulfanilamide in the treatment of otitis media are not clear. There is some question as to the wisdom of its indiscriminate use. When myringotomy is definitely indicated, sulfanilamide should perhaps not be used to the exclusion of operative intervention. This would appear especially true when the organism is not known. In many cases acute otitis media treated early with sulfanilamide subsides completely without suppuration or other complications. Often if suppuration does occur it subsides in twenty-four to seventy-two hours. We have also observed cases in which chronic or recurrent suppurative otitis media that had resisted other forms of therapy cleared up when the drug was used. It is impossible to say how often the development of an infection of the mastoid has been prevented. In many instances the drug apparently aborts what appears to be early mastoiditis. There is no doubt that in many cases early infection of the mastoid which would have required operation before the advent of the drug has subsided with sulfanilamide therapy. It often is justifiable to give sulfanilamide or neoprontosil a trial of twenty-four hours or more before surgical therapy is resorted to, except when the condition is critical. Our sulfanilamide-treated patients have had a shorter convalescence than those not so treated.

However, we wish to emphasize that to be effective the drug must be given in large doses, the earlier in the disease the better. The absorption of the drug by bone is much less than that by other tissues in the body. For this reason, sulfanilamide is less effective against bone infection than elsewhere. It is therefore important that sulfanilamide or neoprontosil be used as an adjunct rather than a substitute for surgical procedure in the treatment of mastoiditis. The invading organism must, of course, be one that is susceptible to the drug. The com-

66. (*a*) Hageman, P. O., and Blake, F. G.: Clinical Experience with Sulfanilamide in the Treatment of Beta Hemolytic Streptococcic Infections, Am. J. M. Sc. **195**:163, 1938. (*b*) Smith, A.: Chemotherapy of Streptococcal Infections, Particularly Streptococcal Tonsillitis, Lancet **2**:1064, 1937. (*c*) Footnote 20. (*d*) Brennemann.[79] (*e*) McIntosh, Wilcox and Wright.[80] (*f*) Carey.[81]

plications of septicemia and meningitis will be taken up under their appropriate headings.

(*c*) Tonsillitis and Cervical Adenitis. These conditions usually respond well to sulfanilamide, prontosil soluble (neoprontosil), and proseptosine, providing the invading organism is susceptible (Hageman and Blake,[66a] and Smith[66b]). Marked cervical adenitis, especially of the acute type, has often been found to recede rapidly but recurs unless the drug is continued over a prolonged period.

(*d*) Meningitis. Few conditions have shown as remarkable a response to a drug as has streptococcic meningitis to sulfanilamide and its derivatives. Comparatively few proved recoveries from streptococcic meningitis were reported in the literature before the advent of these drugs. Trachsler and his associates[67] found 110 recoveries recorded. Of their own series of 71 patients with streptococcic meningitis treated by other methods, only 2 recovered. Of 7 treated with sulfanilamide, neoprontosil and serum, 4 recovered. Neal and Appelbaum[68] cited 15 recoveries among 274 patients treated before the advent of sulfanilamide. In short, the mortality from beta hemolytic streptococcic meningitis prior to the use of sulfanilamide was approximately 95 per cent.

With the introduction of sulfanilamide numerous recoveries have been reported. Silverthorne and Brown[69] treated 93 patients without sulfanilamide, and only 1 recovered. Of 9 patients treated with sulfanilamide and prontosil (neoprontosil), 6 also with mastoidectomy, 5 recovered. Patterson[70] stated that Appelbaum, "reporting for the Meningitis Commission," said that among 256 patients with bacteriologically proved streptococcic meningitis treated by various methods there were only 15 recoveries. Of 12 patients treated with prontosil (neoprontosil), 9 recovered. Debré and associates[71] reported 3 cases in which meningitis of otitic origin was treated successfully with sulfanilamide. Hubert[72] also reported 3 cases in which recovery occurred.

67. Trachsler, W. H.; Franenberger, G. S.; Wagner, C., and Mitchell, A. G.: Streptococcic Meningitis, J. Pediat. **11**:248, 1937. Mitchell, A. G., and Trachsler, W. H.: Report on the Use of Sulfanilamide and Its Derivatives at the Childrens Hospital of Cincinnati, J. Pediat. **11**:183, 1937.

68. Neal, J. B., and Appelbaum, E.: Experience with Sulfanilamide in Meningitis, Am. J. M. Sc. **195**:175, 1938.

69. Silverthorne, N., and Brown, A.: Treatment of Meningitis Due to Hemolytic Streptococci with Sulfanilamide, J. Pediat. **12**:504, 1938.

70. Patterson, D. C.: Experience with Prontosil and Prontylin, J. Connecticut M. Soc. **1**:358, 1937.

71. Debré, R.; Marie, J.; Thiroloix, P., and Grenet: Méningites streptococciques guéries par le traitement sulfamidé, Presse méd. **46**:1058, 1938.

72. Hubert, C.: Traitement des méningites post-otitiques à streptocoques et à "Pneumococcus mucosus" par le para-aminophénylsulfamide (1162 F), Presse méd. **46**:771, 1938.

and Weinberg, Mellon and Shim [73] reported 2 cases in which cure was obtained with sulfanilamide and prontosil (neoprontosil). Of 26 patients treated with prontosil (neoprontosil) and sulfanilamide, Appelbaum [74] reported that 21 recovered. He stated the belief that better results are obtained by use of both drugs. Flake and Carey [75] reported recoveries after the use of sulfanilamide and prontosil (neoprontosil) in 6 patients with complications of beta hemolytic streptococcic otitis media or mastoiditis, 3 of whom had meningitis. Before using sulfanilamide Neal [76] found hemolytic streptococcic meningitis fatal in 95 per cent of her cases. After the use of sulfanilamide and prontosil (neoprontosil) the mortality dropped to 20 per cent in 27 cases. Schwentker and associates [77] reported 3 recoveries in 4 cases of hemolytic streptococcic meningitis treated only with sulfanilamide and prontosil solution (neoprontosil), while none of 37 patients treated by other methods recovered. Of 5 patients treated with sulfanilamide and prontosil (neoprontosil) by Hageman and Blake,[66a] 2 recovered. Numerous other case reports of recoveries following the use of sulfanilamide and its derivatives have appeared in the literature.

The consensus is that therapy should be intraspinal and subcutaneous as well as oral. Sulfanilamide and neoprontosil have also been used intravenously. If sulfanilamide can be taken by mouth 1 Gm. or more per 20 pounds (9.1 Kg.) of body weight up to 100 younds (45 Kg.) of weight is administered during the first twenty-four hours, in four doses at six hour intervals. The 1 per cent solution of sulfanilamide is given intraspinally every twelve to twenty-four hours, the amount being about 5 cc. less than the amount of spinal fluid withdrawn. If the drug is not tolerated when given by mouth, the 1 per cent solution can be given by hypodermoclysis in a dose of 100 cc. per 40 pounds (18.1 Kg.) of body weight every eight to twelve hours. Neoprontosil can be used alone or with sulfanilamide in doses of 1 cc. per pound

73. Weinberg, M. H.; Mellon, R. R., and Shim, L. E.: Two Cases of Streptococcic Meningitis Treated Successfully with Sulfanilamide and Prontosil, J. A. M. A. **108**:1948 (June 5) 1937.

74. Appelbaum, E.: Symposium: What Is Justifiable to Do in Otitic Meningitis? Sulfanilamide and Related Compounds in the Treatment of Meningitis Secondary to the Ear and Sinus Infections, Laryngoscope **48**:482, 1938.

75. Flake, C., and Carey, B.: Sulfanilamide and Derivatives in the Treatment of Beta Hemolytic Streptococcic Infections of Middle Ear and Mastoid, New England J. Med. **217**:1033, 1937.

76. Neal, J. B.: Treatment of Acute Infections of the Central Nervous System with Sulfanilamide, J. A. M. A. **111**:1353 (Oct. 8) 1938.

77. Schwentker, F. F.; Clason F. P.; Morgan, W. A.; Lindsay, J. W., and Long, P. H.: Use of Para-Amino-Benzene-Sulphonamide or Its Derivatives in the Treatment of Beta Haemolytic Streptococcal Meningitis, Bull. Johns Hopkins Hosp. **60**:297, 1937.

(0.45 Kg.) of body weight per twenty-four hours, administered at six hour intervals. Neoprontosil can also be given intraspinally with safety.

Schwentker and associates [77] advocated the following doses of an 0.8 per cent solution of sulfanilamide: 100 cc. for a patient weighing up to 40 pounds, 200 cc. for 40 to 80 pounds (36.3 Kg.), 300 cc. for 80 to 120 pounds (54.4 Kg.) and 400 cc. for over 120 pounds, to be given subcutaneously every eight to twelve hours. This dosage is continued until the spinal fluid has been normal for forty-eight hours. Intraspinal treatment is then stopped, and the oral, subcutaneous or intramuscular therapy is decreased one third. With clinical improvement therapy is further decreased, and it is stopped within the next several days. The spinal fluid usually becomes normal within thirty-six to seventy-two hours after therapy is started. Appelbaum [74] stated the belief that both sulfanilamide and prontosil (neoprontosil) are more effective than either alone. Neal [76] advocated giving by mouth or by injection 5 cc. or less of prontosil (neoprontosil) every four hours to young children and 10 cc. every four hours to older children and adults, in addition to administering 5 to 15 grains (0.32 to 0.97 Gm.) of sulfanilamide orally every four to six hours. If sulfanilamide is to be effective, a concentration in the blood stream of about 10 to 15 mg. per hundred cubic centimeters, and even higher in critically ill patients, is usually necessary.

(*e*) Peritonitis. Primary streptococcic peritonitis is a serious disease. Horsley and Chapman [78] reported a case of primary streptococcic peritonitis in a boy of 13 years who recovered after operative drainage and the use of a total of 100 cc. of prontosil (neoprontosil) and 20.8 Gm. of sulfanilamide. Brennemann,[79] reported recovery of a 9 year old child who was operated on and received 20 cc. of prontosil (neoprontosil) and 15 Gm. of sulfanilamide over six days. McIntosh, Wilcox and Wright [80] reported recovery of 2 patients 1 year old who received 15 to 20 cc. of prontosil (neoprontosil) and 2.4 Gm. of sulfanilamide daily, doses of the latter being gradually decreased. Four patients, 2 months, 16 months, 3½ years and 10 years of age, treated by Carey [81]

78. Horsley, J. S., and Chapman, D. G.: Primary Streptococcic Peritonitis Treated with Sulfanilamide, South. M. J. **31**:999, 1938.

79. Brennemann, J.: Report on Sulfanilamide from the Children's Memorial Hospital of Chicago, J. Pediat. **11**:238, 1937.

80. McIntosh, R.; Wilcox, D. A., and Wright, F. H.: Results of Sulfanilamide Treatment at the Babies Hospital, New York City: Survey of Fifty-Eight Cases Observed Prior to June 10, 1937, J. Pediat. **11**:167, 1937.

81. Carey, B. W., Jr.: The Use of Para-Aminobenzenesulfonamide and Its Derivatives in the Treatment of Infections, Due to β Streptococcus Hemolyticus, Meningococcus, and Gonococcus: Report of Thirty-Eight Cases, J. Pediat. **11**: 202, 1937.

died. All had incision and drainage of the abdomen. Two patients received prontosil (neoprontosil) and 2 prontosil (neoprontosil) and sulfanilamide.

(*f*) Septicemia. When due to hemolytic streptococcic infection this is often fatal. In 166 cases analyzed by Longcope [82] 125 deaths occurred, a fatality rate of 75.3. This corresponds to the figure given by Keefer, Ingelfinger and Spink,[83] who in a series of 246 patients found the mortality to be 72 per cent. The use of sulfanilamide against streptococcic septicemia has shown fairly good results. Robinson [84] reported a cure with prontosil [84a] and sulfanilamide in a boy aged 7 years. Scal [85] reported a case of streptococcic septicemia following acute sinusitis which was cured with sulfanilamide and prontosil (form not specified). Carey [81] reported recovery of 5 patients (3 aged 3 years, 1 aged 1 year and 1 aged 9 years) who received sulfanilamide or sulfanilamide and prontosil (neoprontosil). Brennemann [79] reported recovery in a 7 year old patient with sulfanilamide. McCarthy [86] and Hussey [87] also reported recoveries. In some cases mastoiditis, sinusitis, thrombosis or meningitis which respond to sulfanilamide therapy was complicated by septicemia.

(*g*) Scarlet Fever. Varying reports have appeared in the literature concerning the value of sulfanilamide in the treatment of scarlet fever. Of these, some have been favorable, and others, less so. Hoyne and Bailey [88] in treating 125 patients with sulfanilamide during the fourth week of the disease were unable to find any greater decrease in the number of hemolytic streptococcus carriers than in the controls. Our own investigations have failed to show any favorable action of sulfanilamide in reducing the number of positive cultures of material from

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82. Longcope, W. T.: Problems Relating to the Invasive Properties of the Hemolytic Streptococci and Their Control by Sulphanilamide (Nathan Lewis Hatfield Lecture), Am. J. M. Sc. **195**:577, 1938.

83. Keefer, C. S.; Ingelfinger, F. J., and Spink, W. W.: Significance of Hemolytic Streptococcic Bacteremia: Study of Two Hundred and Forty-Six Patients, Arch. Int. Med. **60**:1084 (Dec.) 1937.

84. Robinson, G. L.: A Case of Streptococcal Septicaemia Treated with Prontosil, Lancet **1**:509, 1937.

84a. Robinson specified "Prontosil (Red)," which usually is a name for the original prontosil. He gave the concentration of the solution, however, as "100 c. cm. = 2.5 grammes," the concentration usually employed with neoprontosil.

85. Scal, J. C.: Septicemia Following Acute Sinusitis Treated with Sulfonamide Compounds, New York State J. Med. **37**:1147, 1937.

86. McCarthy, J. D.: Prontosil and Prontylin, Nebraska M. J. **22**:186, 1937.

87. Hussey, H. H.: Probable Bacterial Endocarditis Apparently Cured with Sulphanilamide: Report of a Case, M. Ann. District of Columbia **6**:275, 1937.

88. Hoyne, A. L., and Bailey, J. H.: Use of Sulfanilamide in the Treatment of Streptococcic Carriers, Arch. Pediat. **54**:731, 1938.

the throat after scarlet fever. Schwentker and Waghelstein [89] found no significant difference in the course, duration and complications of scarlet fever after the use of sulfanilamide. McCarthy [90] reported that sulfanilamide cured a streptococcic infection in the blood stream complicating scarlet fever. In his series of 200 cases of scarlet fever Patterson [70] noticed a drop in the fever within thirty-six to forty-eight hours after sulfanilamide therapy. He found that the rash faded rapidly, while the amount of peeling and the incidence of complications were reduced. Mitman [90] obtained good results in 59 cases of erysipelas and no appreciable results in 355 cases of scarlet fever after the use of proseptasine (parabenzylaminobenzenesulfonamide). Peters and Havard [91] treated 150 patients with proseptasine and compared them with 150 controls, 56 of whom received antitoxin. Complications occurred in 35 per cent of the former group as compared with 56 per cent of the latter. The authors suggested a combination of the drug and antitoxin as the treatment of choice. Sako, Dwan and Platou [92] found no difference in the rate or time of recovery from the acute toxic phase of scarlet fever in a sulfanilamide-treated group of 100 patients as compared with a nontreated group of controls. They found, however, that only 8 per cent of the treated patients had complications, as compared with 41 per cent of the controls. Because serum, either convalescent or commercial, strikingly modifies the toxemia, they advocated the use of serum and sulfanilamide as the treatment of choice. None of 60 persons exposed to scarlet fever by contact who received sulfanilamide contracted the disease. This was not their experience with serum prophylaxis. In the treatment of scarlet fever they advocated a dose of 0.05 Gm. of sulfanilamide per pound of body weight for the first day and a maintenance dose of 0.03 Gm. per pound for an average of twelve days.

(*h*) Streptococcic Pleurisy and Empyema. There have been several favorable reports on the treatment of streptococcic pleurisy and empyema with sulfanilamide and its derivatives. De Sèze [93] reported 2 cases of streptococcic empyema in infants successfully treated with sulf-

89. Schwentker, F. F., and Waghelstein, J.: Use of Sulfanilamide in Scarlet Fever, Baltimore Health News **15**:4, 1938.

90. Mitman, M., in discussion on Treatment of Bacterial Diseases with Sulphanilamide and Its Congeners, Brit. M. J. **2**:929, 1937.

91. Peters, B. A., and Havard, R. V.: Chemotherapy of Streptococcal Infections with *p*-Benzylamino-Benzene-Sulphonamide, Lancet **1**:1273, 1937.

92. Sako, W.; Dwan, P. F., and Platou, E. S.: Sulfanilamide and Serum in the Treatment and Prophylaxis of Scarlet Fever, J. A. M. A. **111**:995 (Sept. 10) 1938.

93. de Sèze: Traitement des pleurésies purulentes streptococciques par le p-amino-phényl-sulfamide, Presse méd. **46**:1120, 1938.

anilamide. Fleming [94] reported 1 case in which recovery occurred with aspiration and the use of sulfanilamide. Brown [95] successfully treated 2 patients with streptococcic empyema by the intrapleural injection of 5 cc. of prontosil soluble (neoprontosil). In 1 of these cases he had given prontosil tablets (the original prontosil) orally for four days without results. Weill-Hallé and co-workers [96] treated a 3 month old infant who had hemolytic streptococcic empyema with 1 Gm. of sulfanilamide orally and a similar amount by suppository. Although there was clinical improvement, the pleural fluid still contained hemolytic streptococci. Twenty-four hours after the injection of 4 cc. of an aqueous solution of soluseptasine (disodium *p* [γ-phenylpropylamino]-benzenesulfonamide-α-γ-disulfonate) the pus became sterile, and the patient recovered promptly. They were equally successful in treating a 33 day old infant and a baby 5 months of age by the same method. Gay and Clark [97] in working with rabbits were able to prevent the evolution of an invariably fatal streptococcic empyema by giving sulfanilamide subcutaneously in repeated large doses. They found that the pleural exudate of treated animals inhibited the growth of streptococci in vitro.

It appears from these reports that sulfanilamide may be of considerable value in the treatment of empyema in young infants.

(*i*) Ludwig's Angina. Fulghum [98] reported the case of a 3 year old child with Ludwig's angina which had developed from a pimple on the chin from which streptococci were cultured. This subsided without suppuration or surgical intervention after intramuscular administration of eleven doses of "2.5 per cent sulfanilamide" (probably neoprontosil was used). The total amount was 36.5 cc., 30.5 cc. being given during the first two days. Clark [99] reported cure of Ludwig's angina with sulfanilamide in 1 case.

(*j*) Puerperal Sepsis. Any evaluation of a drug used in the treatment of puerperal sepsis of hemolytic streptococcic origin is difficult, as the virulence of the organism may vary considerably. A comparison

94. Fleming, J. B.: Streptocide for Streptococcal Empyema, Brit. M. J. **1**:1281, 1937.

95. Brown, J. L.: Prontosil by the Intrapleural Route: Two Cases of Streptococcal Empyema, Brit. M. J. **1**:1157, 1937.

96. Weill-Hallé, B.; Lautmann, L.; Cochemé, R., and Marquézy: Pleurésie purulente à streptocoque hémolytique: Guérison rapide par les sulfamides, Presse méd. **46**:1350, 1938.

97. Gay, F. P., and Clark, A.: Mode of Action of Sulfanilamide in Experimental Streptococcic Empyema, J. A. M. A. **109**:2100 (Dec. 12) 1937.

98. Fulghum, J. E.: Sulfanilamide Treatment of Ludwig's Angina, U. S. Nav. M. Bull. **36**:58, 1938.

99. Clark, W. D.: Infection Treated with Sulfanilamide, Northwest Med. **36**:349, 1937.

of a large series of patients treated with sulfanilamide (and its derivatives) and an equally large number of controls, given in the critical report of Colebrook and his associates,[100] is most valuable. In their first series, which comprised 38 cases of puerperal sepsis, the mortality rate following the use of prontosil (the original prontosil) and prontosil soluble (neoprontosil) was 8 per cent, as compared with rates of 22 to 26.3 per cent in previous cases. In their final total of 199 cases of hemolytic streptococcic infections in puerperal sepsis treated with sulfanilamide, prontosil or sulfamidochrysoidine (the original prontosil) or prontosil (neoprontosil), or with a combination their mortality was 5.5 per cent, as compared with 22.8 per cent in the previous five years. They stated that they considered the prontosils (our term) slightly better than sulfanilamide. Foulis and Barr [101] reported a mortality rate of 1.4 per cent in 70 cases of puerperal sepsis, in 22 of which treatment with sulfanilamide was given (and in 4 cases occasional injections of prontosil soluble [neoprontosil] also) and in the other 48 of which the condition was not considered sufficiently serious for chemotherapy. The mortality rate for 1,988 patients observed between 1931 and 1936 who were not treated with sulfanilamide was 13.5 per cent. In Brown's [102] experience the mortality of streptococcic puerperal infections was reduced from 23.5 to 6.6 per cent by the use of prontosil (term seems to be used in a general sense). In cases in which the condition was complicated by septicemia the mortality was reduced from 87.5 to 28.6 per cent. Of 30 patients with puerperal postabortion hemolytic streptococcic infection to whom Williams [103] gave oral medication,[103a] only 6 died, and of 23 patients with infections not due to hemolytic streptococci who were similarly treated, only 3 died.

Williams [103] used the drug [103a] prophylactically by giving alternate obstetric patients 19 Gm. over several days. The incidence of puerperal infection was the same in the two groups, but the most seriously ill patients were in the nontreated group. Johnstone [104] reported uterine infections in 6.2 per cent of a group of obstetric patients given 5 grain (0.32 Gm.) tablets of sulfanilamide or 7½ grain (0.49 Gm.) tablets

100. Colebrook, L., and Purdie, A. W.: Treatment of One Hundred and Six Cases of Puerperal Fever by Sulphanilamide (Streptocide), Lancet **2**:1291, 1937. Colebrook and Kenney.[35c]

101. Foulis, M. A., and Barr, J. B.: Prontosil Album in Puerperal Sepsis, Brit. M. J. **1**:445, 1937.

102. Brown, D. E., in discussion on Prontosil in Puerperal Infection, Brit. M. J. **2**:230, 1937.

103. Williams, B.: Prontosil in Obstetrics, Lancet **2**:83, 1937.

103a. It is not clear from the report whether sufanilamide or the original prontosil was used.

104. Johnstone, R. W.: Prophylactic Use of Sulphonamide Preparations in Obstetric Practice, Brit. M. J. **1**:562, 1938.

of proseptasine (parabenzylaminobenzenesulfonamide) after delivery (2 tablets three times a day for four days and then 1 tablet three times a day for three days). For obstetric patients of the three previous years, used as controls, the morbidity was 8.2, 9.5 and 6.7 per cent, respectively. In other words, there was no significant difference. MacLaughlin [105] also suggested the use of sulfanilamide for prophylaxis in midwifery. His conclusions were based on 581 pregnant women who received 0.5 Gm. of the drug four times a day for four days on admission to the hospital for delivery. The incidence of puerperal infection as evidenced by fever was 1.7 per cent, in contrast to 3.5 per cent in 574 controls. The wisdom of such prophylaxis has not yet been established.

(k) Mastitis. Brown [102] treated mastitis with prontosil (form not stated) in 21 cases. In only 1 case was incision necessary; in the other 20 cases there was complete resolution. Of 18 patients treated before sulfanilamide was available 9, or 50 per cent, required incision.

B. Anaerobic Beta Hemolytic Streptococcus: Smith and associates [106] reported the case of a 21 year old woman with meningitis of otitic origin due to an anaerobic beta hemolytic streptococcus who recovered after mastoidectomy and large doses of prontosil (neoprontosil), from 15 to 30 cc. every eight hours, followed with sulfanilamide given by mouth. Recovery in case of concurrent puerperal anaerobic streptococcic and staphylococcic septicemia treated with sulfanilamide and streptococcus and staphylococcus serum was reported by Starkie and Wishart.[107]

Sulfanilamide in sufficient dosage is the treatment of choice in all cases of hemolytic streptococcic infection.

C. Nonhemolytic Streptococcus: The effect of sulfanilamide and its derivatives in nonhemolytic streptococcic infections has been far from encouraging. Buttle [108] found that sulfanilamide was not effective in cases of nonhaemolytic streptococcic endocarditis, although of the strains isolated in these cases all but one (Streptococcus faecalis) were susceptible in vitro. Helmholz [109] found Str. faecalis resistant to sulfanilamide

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105. MacLaughlin, J. H.: Sulphonamide for Prophylaxis in Midwifery, Brit. M. J. **1**:757, 1938.

106. Smith, F. W.; Mayer, K. F.; Agerty, H. H.; Fowler, R. H., and Layton, W. C.: Anaerobic Beta Hemolytic Streptococcic Meningitis of Otitic Origin Treated with Sulfanilamide and Culminating in Complete Recovery, J. A. M. A. **110**:887 (March 19) 1938.

107. Starkie, J., and Wishart, G. N. M.: Concurrent Puerperal Anaerobic Streptococcal and Staphylococcal Septicaemia with Recovery, Brit. M. J. **2**:178, 1938.

108. Buttle, G. A. H., in discussion on Treatment of Bacterial Diseases with Sulphanilamide and Related Substances, Lancet **2**:1076, 1937.

109. Helmholz, H. F.: Urinary Infections in Infancy and Childhood, J. A. M. A. **111**:1719 (Nov. 5) 1938.

therapy in urinary infections. Greey [110] found sulfanilamide and the prontosils bacteriostatic to strains of Streptococcus viridans isolated in cases of bacterial endocarditis. A case of subacute infectious endocarditis treated with large doses of prontosil (neoprontosil) and sulfanilamide was reported by Major and Leger.[111] The patient had all the clinical evidence of bacterial endocarditis, and blood cultures were repeatedly positive for Str. viridans. With treatment the blood cultures became negative and the temperature normal. The patient, however, died of cardiac decompensation. At autopsy the blood cultures were still negative, and healing vegetative endocarditis was present. A case of Str. viridans septicemia with rapid complete recovery was reported by Christie.[112] The patient received six doses of prontosil (neoprontosil), 5 cc. at intervals of six hours, and 10 grains (0.64 Gm.) of sulfanilamide four times a day. No results were obtained by Kubitski [113] in a similar case. A case in which nonhemolytic streptococcic septicemia was cured with prontosil (neoprontosil) was reported by Bollinger and Efflen.[114]

Love [115] reported a cure of nonhemolytic streptococcic meningitis. The patient, who was 65 years old, received 1,045 grains (67.71 Gm.) of sulfanilamide and 275 cc. of prontosil (neoprontosil) in eleven days. Three patients with meningitis due to a nonhemolytic streptococcus were treated by Appelbaum [74] with recovery in 1 case.

For the most part the therapeutic results of treatment of nonhemolytic streptococcic infections with sulfanilamide have been poor, but we believe that a few recoveries can be attributed to the use of the drug.

2. *Meningococcic Infections.*—A. Meningococcic Meningitis and Septicemia: Investigations have shown that sulfanilamide and its derivatives are highly effective in the treatment of diseases due to the micrococcus. This appears to be especially true in the treatment of meningococcic infections. Banks [116] treated 59 patients, 10 of whom were infants, with meningococcus serum and with sulfanilamide. The mortality rate was 11.8, and the spinal fluid usually became sterile in

110. Greey, P. H.: Experimental Studies with Sulfanilamide and Other Compounds, Canad. M. A. J. **39**:12, 1938.

111. Major, R. H., and Leger, L. H.: Recovery from Subacute Infectious Endocarditis Following Prontosil Therapy, J. A. M. A. **111**:1919 (Nov. 19) 1938.

112. Christie, W. B.: Use of Prontosil and Prontylin in Streptococcus Viridans Septicemia with Recovery, M. Rec. **146**:489, 1937.

113. Kubitski: Treatment of Local and General Infection of Lymphogranuloma Inguinale with Prontosil, Deutsche Militärarzt **3**:116, 1938.

114. Bollinger H. A., and Efflen, L. R.: Streptococcic Septicemia, Ohio State M. J. **34**:399, 1938.

115. Love, J. W.: Non-Hemolytic Streptococcic Meningitis, J. Lab. & Clin. Med. **23**:482, 1938.

116. Banks, H. S.: Serum and Sulphanilamide in Acute Meningococcal Meningitis: Preliminary Survey Based on One Hundred and Thirteen Cases, Lancet **2**:7, 1938.

twenty-four hours. For 16 patients treated with the drug alone he reported 15 recoveries. For 38 patients (none of them infants) treated with specific serum alone the mortality rate was 16 per cent. He advised the combined use of serum and sulfanilamide as the best form of treatment. Eldahl [117] treated 12 children under 4 years of age with an 0.8 per cent solution of sulfanilamide both intramuscularly and intrathecally. The mortality was 25 per cent, as compared with 70 per cent before such therapy. Bickel [118] reported on 3 patients successfully treated with large doses of sulfanilamide by mouth. For 1 apparently hopelessly ill patient 80,000 units of specific antitoxin was also used. Willien [119] treated 6 patients, 1 of whom had recurrent meningococcic meningitis, with initial doses of an 0.8 per cent solution of sulfanilamide in amounts of 0.05 Gm. of sulfanilamide per kilogram of body weight. His patients were also given 1 Gm. of sulfanilamide or less orally every four hours, the dose depending on the age and size of the patient. Jewesbury [120] treated 6 patients who had severe meningococcic meningitis with serum, with sulfanilamide, prontosil (neoprontosil), soluseptasine and prontosil rubrum (the original prontosil), by mouth, with 100 per cent recovery. Schwentker, Gelman and Long [121] treated 10 patients ranging from 1 year to 34 years of age with an 0.8 per cent solution of sulfanilamide in a physiologic solution of sodium chloride. This was given intraspinally in amounts of 10 to 30 cc. (5 to 10 cc. less than the amount of spinal fluid withdrawn). In addition, 100 cc. of this solution was given subcutaneously for each 40 pounds (18.1 Kg.) of body weight. This therapy was repeated every twelve hours for two days and then once a day. With severe involvement the subcutaneous injections were continued for several days. In no instance was the organism recovered from the spinal fluid after the third day. There was only 1 death, the patient succumbing to pneumonia after the spinal fluid had been normal for three days. Recently Waghelstein [122] reported 106 cases of meningococcic meningitis treated with sulfanilamide alone or combined with specific serum. He used a 1 per cent solution of the powdered sulfanilamide in a physio-

117. Eldahl, A.: Intrathecal Sulphanilamide in Meningococcal Meningitis, Lancet **1**:712, 1938.

118. Bickel, R. D.: Use of Sulfanilamide in Meningococcus Meningitis, Virginia M. Monthly **65**:293, 1938.

119. Willien, L. J.: Sulfanilamide Therapy in Meningococcic Meningitis, J. A. M. A. **110**:630 (Feb. 26) 1938.

120. Jewesbury, E. C. O.: The Use of Sulphanilamide in the Treatment of Meningococcal Meningitis, Lancet **1**:1262, 1938.

121. Schwentker, F. F.; Gelman, S., and Long, P. H.: Treatment of Meningococcic Meningitis with Sulfanilamide: Preliminary Report, J. A. M. A. **108**:1407 (April 24) 1937.

122. Waghelstein, J. M.: Sulfanilamide in the Treatment of One Hundred and Six Patients with Meningococcic Infections, J. A. M. A. **111**:2172 (Dec. 10) 1938.

logic solution of sodium chloride for subcutaneous and intrathecal injections. The drug was given in this manner until the patient could tolerate it when given by mouth. Among all patients treated there were 19 deaths, a mortality of 18 per cent. Of those who had adequate sulfanilamide therapy only 12 died, a case fatality of 12 per cent.

Weill-Hallé and associates [123] reported the recovery of a 9 month old infant who was given 55 cc. of serum and then sulfanilamide. Two cases were reported by Winchester; [124] in 1 the condition was not improved with the use of serum but recovery promptly occurred when soluseptasine was used. Murez, Chirle and Quequiner [125] in commenting on the comparative methods of treating cerebrospinal meningitis gave the following results: 49 serum-treated patients, mortality 22.4 per cent; 23 patients treated with serum and with sulfanilamide perorally, mortality 8.69 per cent; 54 patients receiving sulfanilamide intraspinally, mortality 14.8 per cent, and 271 patients treated perorally with sulfanilamide alone, mortality 10.7 per cent.

Sulfanilamide has also been successfully used in the treatment of meningococcic septicemia not accompanied by meningitis. One patient who was treated with sulfanilamide alone and recovered was reported on by Schwentker, Gelman and Long.[121] Zendel and Greenberg [126] reported on 2 patients with septicemia, both of whom recovered. In 1 case there was no response to massive doses of specific serum, but recovery was prompt when prontosil (neoprontosil) and sulfanilamide were given. The temperature was normal forty-eight hours after the treatment was begun, and two blood cultures made after that time were sterile. The patient had received 40 cc. of prontosil (neoprontosil) and 8.45 Gm. of sulfanilamide during the first forty-eight hours, and 0.65 Gm. of sulfanilamide three times a day for the next three days. In the second case the temperature became normal in sixty hours and the blood was sterile after twenty-four hours. In this case no serum was used, but 100 cc. of prontosil (neoprontosil) and 5.2 Gm. of sulfanilamide were given during the first forty-eight hours of treatment, followed by 0.65 Gm. of sulfanilamide three times a day for the next six days. A case of chronic meningococcemia without meningitis and with recovery was

123. Weill-Hallé, B.; Cochemé, R., and Lautmann, L.: Méningite purulente à méningocoques: Guérison après sérothérapie et chimiothérapie associées, Presse méd. **46**:477, 1938.

124. Winchester, A. H.: Sulphonamides for Meningococcal Meningitis, Brit. M. J. **2**:70, 1938.

125. Murez, G.; Chirle, H., and Quequiner, A.: Comparative Methods of Treatment of Cerebrospinal Meningitis, Presse méd. **46**:113, 1938.

126. Zendel, J. F., and Greenberg, D.: Meningococcemia: Treatment with Sulfanilamide and Prontosil—Report of Two Cases, New York State J. Med. **37**: 1744, 1937.

reported by Dimson.[127] The blood became sterile and the temperature normal within twenty-four hours after use of 2-(paraaminobenzenesulfonamido)-pyridine (sulfapyridine) in doses of 2 to 4 Gm. a day. There are numerous other case reports in the literature.[128]

We found only 1 report on the prophylactic use of sulfanilamide in a case of exposure to meningococcic infection. Bickel[118] gave 15 grains (0.97 Gm.) of sulfanilamide three times a day for six days to 28 persons who had almost continuous exposure to patients with meningococcic meningitis. The disease did not develop in any of these contacts.

Rosenthal, Bauer and Branham[129] found that sulfanilamide had a marked therapeutic action on twenty strains of meningococci of types I, II and III, which they used in infecting mice. Similarly good results were obtained by Banks[116] in patients with infections due to types I and II and, in a few instances, unidentified strains.

The dosage and routes of administration are given in the sections on dosage and on streptococcic meningitis. The best results have been obtained with concentrations of between 5 and 13 mg. of sulfanilamide per hundred cubic centimeters of spinal fluid, although recoveries have been reported with concentrations as low as 1.8 mg. Although many cases of recovery with the use of sulfanilamide alone have been reported, the consensus still favors combined serum and sulfanilamide therapy.

3. *Gonococcic Infections.*—A. Vulvovaginitis: This condition has always been characterized by its resistance to treatment and its marked chronicity. Before the advent of sulfanilamide, injections of estrone (theelin) appeared to be the newest treatment of choice. The work of Hoffman and his associates[130] indicated that more favorable results can be obtained with sulfanilamide than with either local treatments or injections of theelin. In their series of 25 patients, ranging from 3 months to 10 years of age, 7 were cured in an average of seventeen and three-tenths days, 9 in an average of forty-two and nine-tenths days and 2 with additional periods of treatment, while 7 failed entirely to respond to treatment. They gave the drug orally, the dose being ¾ grain (0.045 Gm.) daily per pound of body weight for two days, 9/16 grain (0.032 Gm.) daily per pound of body weight for five days and ⅜ grain (0.024 Gm.) daily per pound of body weight for the following two weeks. A rest of one week followed, and the course of treat-

127. Dimson, S. B.: Chronic Meningococcal Septicaemia Treated with 2-(*p*-Aminobenzenesulphonamido) Pyridine, Lancet **2**:424, 1938.

128. Brennemann,[79] McIntosh, Wilcox and Wright.[80] Carey.[81]

129. Branham, S., and Rosenthal, S. M.: Studies in Chemotherapy, Pub. Health Rep. **52**:685, 1937.

130. Hoffman, A. J.; Schneider, M.; Blatt, M. L., and Herrold, R. D.: Sulfanilamide in the Treatment of Gonorrheal Vulvovaginitis, J. A. M. A. **110**:1541 (May 7) 1938.

ment was repeated as necessary. Holmes, Jones and Gildersleeve,[131] on the other hand, in treating 42 patients with sulfanilamide orally in amounts of 0.6 Gm. per 20 pounds of body weight, found that only 16 were temporarily relieved, and of these, 8 had recurrences. Five patients treated with sulfanilamide suppositories showed no improvement. Gate and Cuilleret,[132] using sulfanilamide in treating this condition in infants, reported cures in all 8 cases of their series.

Martin [134] reported that 2 young girls treated with sulfanilamide and local therapy were cured in seven and fourteen days, respectively. Lloyd, Erskine and Johnson [135] reported 7 cases of vulvovaginitis in children treated with 2-(paraaminobenzenesulfonamido)-pyridine (sulfapyridine), in the form of M & B 693; a favorable response occurred in three days with daily doses of 0.75 to 1.5 Gm.

So far the efficacy of sulfanilamide is not conclusively proved, but the reports indicate much better results than with any other form of therapy. As yet the optimal dosage has not been determined, and it is more than possible that sufficient amounts of the drug for the best results are not being given. Certainly it offers one of the least troublesome forms of therapy and should be given an adequate trial before other forms are used.

B. Ophthalmia Neonatorum: Although the majority of infants with gonococcic infection of the eye recover with local treatment, the usual duration of the disease is between three and four weeks, and irreparable damage may result. Michels,[136] using sulfanilamide in daily doses of 1 grain (0.06 Gm.) per pound of body weight and local treatment by the accepted methods, reported an average duration of five and eight-tenths days in 15 cases. This is in contrast to sixteen and five-tenths days when injections of milk and local treatment were used and twenty-eight and five-tenths days when only routine local care was administered. The ages of the patients were between 5 days and 3 years. Concentrations of sulfanilamide in the blood varied between a trace and 11.2 mg. per hundred cubic centimeters. Willis [137] reported 5 cases of ophthalmia

131. Holmes, J. W.; Jones, J. A., and Gildersleeve, N.: Use of Sulfanilamide in Gonococcal Infections in Children, J. Pediat. **12**:610, 1938.

132. Gate, J., and Cuilleret, P.: Le traitement des vulvo-vaginites gonococciques infantiles par le 1162 F, Presse méd. **46**:923, 1938.

133. Footnote deleted.

134. Martin, R.: Action favorable du sulfamide associá à un traitement local, dans les vulvo-vaginites gonococciques des petites filles, Presse méd. **46**:477, 1938.

135. Lloyd, V. E.; Erskine, D., and Johnson, A. G.: Chemotherapy of Pneumococcal and Other Infections, Lancet **1**:1305, 1938.

136. Michels, M. W.: Sulfanilamide in the Treatment of Gonococcal Ophthalmia in Children, J. Pediat. **13**:527, 1938.

137. Willis, T.: Sulfanilamide in Ophthalmia Neonatorum, Yale J. Biol. & Med. **10**:275, 1938.

neonatorum which responded rapidly to sulfanilamide given in daily doses of 0.2 to 0.23 Gm. per kilogram. He found that a blood concentration of 7 mg. of sulfanilamide per hundred cubic centimeters was necessary for optimal results, and concentrations as high as 20 mg. with a dosage of 0.33 Gm. per kilogram per day were reached. Slobozianu [138] cured 6 patients in four to eighteen days with uliron (dimethyldisulfanilamide) in doses of 1 to 1½ tablets daily. Michie and Webster [139] reported dramatic cures in infants within three days after the use of M & B 693 (sulfapyridine) in doses of 0.25 Gm. given twice daily. Fernández and Fernández [140] reported spectacular cures in 9 cases of gonococcic ophthalmia in adults, 2.6 Gm. of sulfanilamide being given daily for 3 days and 1.95 Gm. on the fourth day. Newman [141] reported 8 cases of ophthalmia in young children cured with sulfanilamide. He used 2.4 Gm. daily for children 5 years of age and 1.5 Gm. for children 1½ years of age for two days and one third of the dose daily for eight more days.

There are other favorable reports of 1 or more cases each in the literature. With no exceptions, sulfanilamide given orally in conjunction with the common forms of local treatment is the therapy of choice as to the rapidity of recovery, the control of the spread of the infection and the prevention of complications which later impair vision. If corneal ulceration is present before therapy is started, although there is rapid healing of the infection, perforation or scarring usually results. This is undoubtedly due to the poor blood supply of the cornea. Treatment is equally successful in newborn and in older patients.

C. Meningitis: Branham, Mitchell and Brainin [142] reported a case of gonococcic meningitis in a 16 year old girl cured by oral and intraspinal administration of sulfanilamide. She received 620 grains (40.18 Gm.) orally during eleven days and 105 cc. of a 1 per cent solution intraspinally during four days. Marvin and Wilkinson [143] reported recovery of an 18 year old boy from gonococcic meningitis which at first was diag-

138. Slobozianu, H.: Die Behandlung der Ophthalmoblenorrhoe mit Uliron, Dermat. Wchnschr. **107**:1089, 1938.

139. Michie, A. M., and Webster, M. H.: Gonococcal Ophthalmia Treated with 2-(*p*-Aminobenzenesulphonamido) Pyridine, Lancet **2**:373, 1938.

140. Fernández, L. J., and Fernández, R. F.: Sulfanilamide in Gonorrheal Ophthalmia: Preliminary Report, Am. J. Ophth. **21**:763, 1938; abstracted, J. A. M. A. **111**:873 (Aug. 27) 1938.

141. Newman, H. W.: Sulfanilamide in Gonorrheal Ophthalmia in Young Children, Texas State J. Med. **33**:585, 1937.

142. Branham, S. E.; Mitchell, R. H., and Brainin, W.: Gonococcic Meningitis, J. A. M. A. **110**:1804 (May 28) 1938.

143. Marvin, H. P., and Wilkinson, W. E.: Gonococcic Meningitis, J. A. M. A. **110**:800 (March 12) 1938.

nosed as meningococcic meningitis and treated with 110,000 units of serum in four days. The patient was then given 0.324 Gm. of sulfanilamide three times a day. This therapy was begun seven days after the onset of symptoms and continued for twelve days, after which the temperature became normal. Four days later the fever returned. Nine days later sulfanilamide was again given, in the same amount, therapy being continued for nine days. One month later the symptoms returned, but the patient recovered completely after the further use of sulfanilamide.

The mortality of gonococcic meningitis with other forms of therapy has been reported to be about 45 per cent.

D. Rheumatism: Brulé, Hillemand and Vildé [144] treated 3 patients who had gonococcic rheumatism with sulfanilamide. In all 3 cases the symptoms subsided within two days. Two patients had relapses, but when the drug was given again the disease subsided completely. In 1 case no other form of therapy had been successful. Bauer and Coggeshall [145] stated that sulfanilamide is the most effective method of treatment for gonococcic arthritis.

E. Urethritis: There are numerous reports in the literature on the treatment of this condition with sulfanilamide. Alyea, Daniel and Harris [146] treated 65 patients with acute gonococcic urethritis with sulfanilamide and obtained a cure in 86 per cent. In contrast, Shih and Hsiung,[147] using 3.6 Gm. of this drug daily for two days, then 2.4 Gm. for two days and 1.2 Gm. for two or three days, obtained the following results: Of 25 patients with acute infection 12 per cent were cured, 8 per cent greatly improved, 36 per cent improved and 44 per cent unimproved. Of 16 patients with chronic infection 6 per cent were cured, 19 per cent were greatly improved, 31 per cent were improved and 44 per cent were unimproved. Harrison [148] stated the opinion that the best results are obtained when administration of "the sulphonamide remedies" is not started until after the third week of the infection. Crean [149] cured 90 of 100 patients treated with sulfanilamide and prontosil soluble (neo-

144. Brulé, M.; Hillemand, P., and Vildé, L.: Deux cas de rhumatisme gonococcique traités par la para-amino-phényl-sulfamide, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:1650, 1937; abstracted, J. A. M. A. **110**:698 (Feb. 26) 1938.

145. Bauer, W., and Coggeshall, H. C.: Sulfanilamide Treatment of Arthritis, Science News Lett. **33**:408, 1938.

146. Alyea, E. P.; Daniel, W., and Harris, J.: Sulfanilamide Therapy in Gonorrhea and Its Complications, South M. J. **31**:395, 1938.

147. Shih, H. E., and Hsiung, J. C.: Treatment of Gonorrhea with Sulfanilamide, Chinese M. J. **53**:455, 1938.

148. Harrison, L. W.: When to Start Sulphonamide Treatment in Gonorrhea, Brit. M. J. **2**:90, 1938.

149. Crean, T. F.: The Use of Prontosil in the Treatment of Gonorrhea, Lancet **2**:895, 1937.

prontosil). Reuter [150] used sulfanilamide in 40 cases of recent infection and obtained cures in 92.5 per cent. In treating 60 patients with chronic infection who had had various forms of therapy, he obtained recoveries in 88 per cent. Dees and Colston,[151] who treated 47 patients suffering from gonococcic infection of the urinary tract with sulfanilamide, reported the following results: Thirty-six patients were cured in five days; in 5 cases the subjective symptoms alone disappeared; in 3 cases there was no response to sulfanilamide, and in 3 cases there was a relapse after an initial prompt response. In 2 of the latter there was subsequent cure with additional courses of the drug. The authors used 4.8 Gm. of sulfanilamide daily for two days, 3.6 Gm. for the next three days and 2.4 Gm. for the following four to eight days.

As gonorrheal urethritis is not a common disease of childhood, only the reports just cited will be included here. The number of cures varies with different authors from about 50 to 95 per cent, the great majority reporting favorable results. It seems evident that all strains of the gonococcus are not equally susceptible to the drug. In many instances the failures were apparently due to insufficient doses or periods of treatment. No definite or optimal standard has yet been reached. Furthermore, there is considerable confusion as to the time after onset of the disease when sulfanilamide therapy should be started. It is felt by some investigators that the best results are obtained with chronic involvement and that treatment should not be started until after the third week of infection. This is especially emphasized in the reports from Germany, where uliron (dimethyldisulfanilamide) is most commonly used. German authors have expressed the belief that this compound has a more specific action on the gonococcus than sulfanilamide, but it apparently produces more severe toxic reactions.

4. *Pneumococcic Infections.*—Until recently these have been treated either symptomatically or with specific serum. The mortality for type I has been estimated as about 20 per cent, for type II about 25 per cent, for type III from 50 to 100 per cent and for group IV, which contains various types, from 5 to 35 per cent. The results obtained with serum have been favorable for type I, fairly favorable for type II and less favorable for type III. Certain types in group IV have responded well to serum therapy. As evident from these figures, infection with the type III pneumococcus carries with it a serious prognosis.

Besides the clinical reports on the use of sulfanilamide against pneumococcic infections there have been many reports of experimental

150. Reuter, F. A.: Use of Sulfanilamide in the Treatment of Gonorrhea, M. Ann. District of Columbia **6**:117, 1937.

151. Dees, J. E., and Colston, J. A. C.: The Use of Sulfanilamide in Gonococcic Infections, J. A. M. A. **108**:1855 (May 29) 1937.

work both in vitro and in animals. Miller [152] produced pneumococcemia in mice with type III Pneumococcus. Specific antibacterial rabbit serum offered complete protection in the infected mice, while sulfanilamide offered no protection, and the use of both serum and sulfanilamide (61.6 mg. in five days) gave results which were variable but in some experiments not as good as those obtained with serum alone. On the other hand, it has been shown by Cooper and co-workers [153] that the lives of rats and mice can be prolonged and often saved by the drug after subcutaneous or intrabronchial inoculation with the type III pneumococcus. Long and Bliss [8] found that sulfanilamide is bacteriostatic against pneumococci of types I, II and III in vitro, but it did not save mice infected intraperitoneally. Bürgers [154] reported that the serum or blood of healthy or pneumococcus-infected animals receiving prontosil I (the original prontosil), prontosil S (neoprontosil) or sulfanilamide showed no stronger bactericidal effect than that of infected animals which received no treatment. He was also unable to demonstrate any bactericidal effect of the drug on pneumococci of type I, II or III in vivo or in vitro. Gross and Cooper [155] reported a mortality of 93 per cent in rats infected with the type I pneumococcus when no treatment was used, 21 per cent with sulfanilamide, 20 per cent with specific type I serum and 14 per cent when serum and sulfanilamide were used at the same time. These same authors found sulfanilamide highly effective against the type II pneumococcus. Kreidler [156] reported that the effects of the drug against type I pneumococcic infections in rabbits were satisfactory. Schmidt [157] found the drug highly effective against type XIV pneumococcic infections in mice.

(a) Meningitis. Reid and Dyke [158] reported a cure in a 7 year old child suffering from pneumococcic meningitis. It was found not to be

152. Miller, J. K.: Preliminary Report on the Action of Immune Serum in Conjunction with Sulfanilamide in Type-III Pneumococcus Infections in Mice, J. Bact. **36**:219, 1938.

153. Cooper, F. B.; Gross, P., and Mellon, R. R.: Action of *p*-Aminobenzenesulfonamide on Type III Pneumococcus Infections in Mice, Proc. Soc. Exper. Biol. & Med. **36**:148, 1937. Gross, P., and Cooper, F. B.: Efficacy of *p*-Aminobenzenesulfonamide in Experimental Type III Pneumococcus Pneumonia of Rats, ibid. **36**: 225, 1937.

154. Bürgers: Chemotherapie der Streptokokkenerkrankungen durch Prontosil, Deutsche med. Wchnschr. **63**:672, 1937.

155. Gross, P., and Cooper, F. B.: Sulfanilamide and Antipneumococcal Serum Therapy in Type I Pneumococcus Infections in Rats, Proc. Soc. Exper. Biol. & Med. **36**:535, 1937.

156. Kreidler, W. A.: Treatment of Pneumococcal Infections in Rabbits with Sulfanilamide, Proc. Soc. Exper. Biol. & Med. **37**:146, 1937

157. Schmidt, L. H.: Use of Sulfanilamide in the Treatment of Type XIV Pneumococcus Infections in Mice, Proc. Soc. Exper. Biol. & Med. **37**:205, 1937.

158. Reid, G. C. K., and Dyke, S. C.: Pneumococcal Meningitis Treated with M. & B. 693: Recovery, Lancet **2**:619, 1938.

of type I, II, III or VII. Treatment in this instance was started six days after the onset; it consisted of giving 1 Gm. of M & B 693 (sulfapyridine) and then 0.5 Gm. at four hour intervals for two days and at six hour intervals for eight days, a total of 22.5 Gm. being given. We recently treated a child suffering from type IV pneumococcic meningitis. With an 0.8 per cent solution of sulfanilamide given intravenously the first day and orally the following day, there was a rapid drop in fever, followed by complete recovery. Allan, Mayer and Williams [159] reported 3 cases, 1 each of type XIV, type XXIX and type XX, in all of which recovery occurred with use of the drug. Finland, Brown and Rauh [160] reported 10 cases in which meningitis was treated with sulfanilamide, alone or with serum, with 6 recoveries. Query [161] successfully treated type VII pneumococcic meningitis with sulfanilamide and serum. In this case the concentration of sulfanilamide in the blood was 23 mg. per hundred cubic centimeters and in the spinal fluid 16 mg. Martin [162] and Young [163] each reported 1 case of pneumococcic meningitis cured with sulfanilamide, 23 Gm. being administered in Young's case. The recovery of a 10 year old girl with type I pneumococcic meningitis was reported by Tixier, Eck and Grossiard.[164] Administration of sulfanilamide by mouth was the only medication; it was begun on the third day of illness. Caldwell and Byrne [165] reported a case in which a 16 year old girl with meningitis was cured with prontosil soluble (neoprontosil) and prontosil tablets (form not specified). A 26 year old man with meningitis was reported as cured with prontosil (form not specified) by Latto.[166] Landon [167] reported a case in which a 5 year old girl with meningitis was cured with administration of 10 cc. of prontosil soluble (neoprontosil) twice daily on

159. Allan, W. B.; Mayer, S., and Williams, R.: Pneumococcus Meningitis with Recovery, Am. J. M. Sc. **196**:99, 1938.

160. Finland, M.; Brown, J., and Rauh, A.: Treatment of Pneumococcic Meningitis, New England J. Med. **218**:1033, 1938.

161. Query, R. Z.: Pneumococcus Type VII Meningitis, Treated with Sulfanilamide and Specific Serum, with Recovery, J. A. M. A. **111**:1373 (Oct. 8) 1938.

162. Martin, R.: Méningite cérébro-spinale à pneumocoque I guérie par le sulfamide (voie buccale), Presse méd. **46**:599, 1938.

163. Young, F.: Pneumococcal Meningitis Treated with Sulphanilamide: Recovery, Brit. M. J. **2**:286, 1938.

164. Tixier, L.; Eck, and Grossiard: Méningite cérébro-spinale à pneumocoque I guérie par le sulfamide (voie buccale), Presse méd. **46**:599, 1938.

165. Caldwell, J. R., and Byrne, P. S.: Recovery from Pneumococcal Meningitis, Brit. M. J. **1**:1204, 1937.

166. Latto, C.: Pneumococcal Meningitis Treated with Prontosil, Brit. M. J. **1**: 566, 1938.

167. Landon, J.: Pneumococcal Meningitis Treated with Prontosil Soluble, Brit. M. J. **1**:844, 1938.

four successive days. Millett [168] used prontosil (neoprontosil) intramuscularly and intrathecally in 20 cc. doses in a case of type III pneumococcic meningitis and septicemia. Although the patient died, the spinal fluid showed only a scant growth of organisms after treatment, while previously the growth had been profuse. The prontosil (neoprontosil) did not cause any irritation to the central nervous system.

In the experience of Neal,[76] pneumococcic meningitis had been almost uniformly fatal for nearly twenty-seven years before she began the use of sulfanilamide. Neal and Appelbaum [169] treated 33 patients with sulfanilamide, with 6 recoveries. In the cases in which recovery occurred the pneumococci were of types XXXI, XXIX, IV, XIII, VI and VII. With type VI rabbit serum was also used and with type VII horse serum. In the fatal cases the organisms were of types I, III, V, VII, VIII, X, XIII, XVIII, XXIII and XXXI and of types numbered above XXXII.

Neal has advised the use of sulfanilamide, prontosil (neoprontosil) and specific serum, when available, with the dosage and methods of administration described in the sections on dosage and streptococcic meningitis.

(*b*) Pneumonia. Heintzelman, Hadley and Mellon [170] in their series of 19 cases of type III pneumococcic pneumonia treated 9 of the patients with sulfanilamide augmented in a few cases with prontosil (neoprontosil). The mortality was 22 per cent. For the 10 patients not treated with the drug the mortality rate was 80 per cent. Another series of 33 patients in the same locality was not treated with the drug. The mortality for the untreated patients of both series was 74 per cent. Millett [168] reported 1 case of type III pneumonia cured with sulfanilamide. Louis [171] treated with sulfanilamide 6 patients who had pneumonia of types I to III, complete recovery occurring in all. Gormly [173] reported that in the treatment of pneumonia of type III or of an undetermined type with sulfanilamide results were sometimes good and at other times disappointing.

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168. Millett, J.: The Intrathecal Use of Prontosil Soluble: Report of a Case of Type III Pneumococcus Meningitis and Septicemia Treated with Prontosil Soluble, with Complete Autopsy Report, J. A. M. A. **109**:2138 (Dec. 25) 1937; Sulfanilamide, New York State J. Med. **37**:1743, 1937.

169. Neal and Appelbaum.[68] Appelbaum.[74] Neal.[76]

170. Heintzelman, J. H. L.; Hadley, P., and Mellon, R. R.: Use of *p*-Aminobenzenesulphonamide in Type III Pneumococcus Pneumonia, Am. J. M. Sc. **193**: 759, 1937.

171. Louis, D. J.: Treatment of Pneumonias with Sulfanilamide, Illinois M. J. **73**:422, 1938.

172. Footnote deleted.

173. Gormly, C. F.: Nonspecific Measures in the Treatment of Pneumonia, Rhode Island M. J. **21**:87, 1938.

Of the derivatives of sulfanilamide, sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine), known by the trade names M & B 693 and dagenan is thought to be more effective than sulfanilamide. Although this drug has been used in Europe for some time, its patent rights have only recently been purchased for the United States. Whitby [174] found this derivative to be more effective than sulfanilamide in protecting mice against pneumococcic infection. He found that against infection with types I, VII and VIII the protection was complete and that with types II, III and V it was high. Encouraging results with compounds with a pyridine nucleus in rabbits which had streptococcic infections were reported by Kolmer and his associates.[175] Telling and Oliver [176] reported a case of massive pneumonia of type III with massive collapse, the patient recovering completely with 2-(paraaminophenylsulfonamido) pyridine (sulfapyridine). They also reported 1 case of type XI pneumonia and hemolytic influenza and 1 of type I pneumonia, in both of which recovery took place with this drug. Evans and Gaisford [177] treated 100 patients who had pneumococcic pneumonia with M & B 693 (sulfapyridine). There were 8 deaths, and empyema developed in 6 cases. In a control series of 100 patients not receiving the drug there were 27 deaths and 1 instance of empyema. In 37 treated patients the temperature became normal within twenty-four hours and in 23 within forty-eight hours. This is in contrast to the control series, in which the temperature returned to normal in twenty-four hours in 16 cases and in forty-eight hours in 18. They also used the drug for 40 children and infants with bronchopneumonia, only 2 deaths occurring. Report of recovery of a critically ill patient with sulfapyridine was made by Christie.[178] Further information on this drug and the recommended dosage will be available only after further investigation.

Sulfanilamide has not been as successful in the treatment of pneumonia as it has been with some other diseases. Large doses are recommended, with the use of specific serum when it is available.

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174. Whitby, L. E. H.: Chemotherapy of Pneumococcal and Other Infections with 2-(*p*-Aminobenzenesulphonamido) Pyridine, Lancet **1**:1210, 1938

175. Kolmer, J. A.; Brown, H.; Raiziss, G. W.; Rule, A. M., and Clemence, A. W.: Chemotherapy of Experimental Streptococcic Infections of Rabbits with Special Reference to Pyridine Compounds and Prontosil Solution, J. Pharmacol. & Exper. Therap. **61**:253, 1937.

176. Telling, M., and Oliver, W. A.: Case of Massive Pneumonia, Type III, with Massive Collapse, Treated with 2-(*p*-Aminobenzenesulphonamido) Pyridine, Lancet **1**:1391, 1938.

177. Evans, G. M., and Gaisford, W. F.: Treatment of Pneumonia with 2-(*p*-Aminobenzenesulphonamido) Pyridine, Lancet **2**:14, 1938.

178. Christie, J. M.: Chemotherapy of Pneumonia, Lancet **2**:281, 1938.

(*c*) Peritonitis. We have been able to find only 1 instance of this condition. In this case, which was reported by Sager and Raffel,[179] the abdomen was opened, and cultures were made, but the organism was not typed. Sulfanilamide was given orally, and recovery occurred promptly.

5. *Infections of the Urinary Tract.*—Sulfanilamide and some of its derivatives are being widely used in the treatment of these infections. Helmholz [109] found sulfanilamide to be effective against practically all urinary infections except those caused by Str. faecalis. According to this investigator the drug can be given in the acute stage of the infection. It is more effective in alkaline urine but acts in acid urine. He found it to be excreted in bactericidal quantities by kidneys so severely damaged that the urea concentrations in the blood were between 75 and 100 mg. per hundred cubic centimeters. Helmholz prescribed 10 grains (0.65 Gm.) per 20 pounds (9.1 Kg.) of body weight with 30 to 60 grains (1.94 to 3.88 Gm.) of sodium bicarbonate per day. The water intake should be slightly decreased. Barr [180] treated pyelitis of pregnancy successfully with sulfanilamide in 64 cases and found it more effective than prontosil soluble (neoprontosil). In 2 cases Albright, Dienes and Sulkowitch [181] obtained periods of temporary cure of pyelitis due to Haemophilus influenzae with sulfanilamide given by mouth. Cultures of the urine later again became positive. All other forms of therapy had not given even temporary relief. Kenny and his co-workers [182] reported 46 cases of infection of the urinary tract with Bacillus coli in which the symptoms subsided within two to five days after the use of sulfanilamide. However, they found that not all strains of B. coli were equally susceptible to sulfanilamide. It is well to keep in mind that urinary infections are in many cases secondary to urinary stasis caused by some anatomic anomaly or other abnormality in the tract. As has been pointed out by Brennemann,[183] the indiscriminate use of sulfanilamide may be dangerous. Without further investigation as to the cause of the infection, sterile urine may give a false sense of

179. Sager, W. W., and Raffel, W.: Case of Pneumococcal Peritonitis Treated with Prontylin, M. Ann. District of Columbia **7**:99, 1938.

180. Barr, A. G.: Sulfanilamide in the Treatment of Pyelitis of Pregnancy, Glasgow M. J. **12**:18, 1938.

181. Albright, F.; Dienes, L., and Sulkowitch, H.: Pyelonephritis with Nephrocalcinosis, J. A. M. A. **110**:357 (Jan. 29) 1938.

182. Kenny, M.; Johnston, F. D.; von Haebler, T., and Miles, A. A.: *p*-Aminobenzenesulphonamide in Treatment of Bacterium Coli Infections of the Urinary Tract, with a Note on the Two-Plate Bacterial Count, Lancet **2**:119, 1937.

183. Brennemann, J.: Personal communication to the authors.

security which leads to serious harm. Intravenous pyelograms and roentgen studies are still indispensable aids in the treatment of urinary diseases.

Sulfanilamide is apparently superior to other drugs in its effect on most infections of the urinary tract, especially those due to B. coli, Bacillus aerogenes, Bacillus proteus, Bacillus typhosus or paratyphosus,[184] some staphylococci or streptococci, except Str. faecalis, beta hemolytic streptococci of Lancefield group D and the small members of group G.[185] The acute symptoms, such as fever and pain, often disappear within twenty-four hours, and the urine may be free of pus in forty-eight hours.

6. *Undulant Fever (Infection with Brucella Abortus, Brucellosis, Bang's Disease).*—Chinn [186] found sulfanilamide bactericidal in vitro in dilutions of 1 to 1,000 and bacteriostatic in dilutions of 1 to 10,000 for both Br. abortus and Brucella suis. Recent reports indicate that sulfanilamide is of great therapeutic value in undulant fever. Welch, Wentworth and Mickle [187] demonstrated marked stimulation of the phagocytic activity of the white blood cells for Brucella when sulfanilamide was used. They stated the belief that since sulfanilamide-treated normal persons and persons infected with other organisms fail to show any change in opsonocytophagic activity for Brucella organisms, the use of this drug in suspected cases of brucellosis should be helpful diagnostically. The effect of the drug is apparently indirect, as it does not have to be present in the blood stream when phagocytosis is demonstrated. The authors expressed the opinion that it acts through stimulation of the defense mechanism of the infected person, producing specific opsonins and thus effecting neutralization of the endotoxic, or aggressive, substance, this process finally resulting in phagocytosis.

Welch and his associates [187] reported 5 cases of undulant fever in adults successfully treated with sulfanilamide (60 to 120 grains [3.88 to 7.78 Gm.] per day). Berger and Schnetz [188] reported 1 case in which this disease was treated successfully with 3 tablets of prontosil (the original prontosil) given daily and an intramuscular injection of prontosil

184. Barer, M.: Typhoid Bacilluria Treated with Sulfanilamide, Lancet **2**: 946, 1937.

185. Bliss, E. A., and Long, P. H.: Failure of Para-Aminobenzenesulfonamide Therapy in Urinary Tract Infections Due to Group D (Lancefield) Beta Hemolytic Streptococci, New England J. Med. **217**:18, 1937.

186. Chinn, B. D.: In Vitro and in Vivo Effect of Sulfanilamide on B. Abortus and B. Suis, Proc. Soc. Exper. Biol. & Med. **38**:732, 1938.

187. Welch, H.; Wentworth, J., and Mickle, F.: Use of Sulfanilamide in the Diagnosis and Treatment of Brucellosis, J. A. M. A. **111**:226 (July 17) 1938.

188. Berger, W., and Schnetz, H.: Ein Behandlungserfolg bei Morbus Bang mit Prontosil, Med. Klin. **33**:594, 1937.

(neoprontosil) three times a week. Traut and Logan [189] treated 2 patients with 30 to 40 grains (1.94 to 2.59 Gm.) of sulfanilamide daily with disappearance of fever within forty-eight hours. Stern and Blake [190] treated 3 patients successfully with sulfanilamide. In 1 case the symptoms and fever disappeared within thirty-six hours after the use of 105 grains (6.79 Gm.) of sulfanilamide. In the other 2 cases the fever subsided in four days with a dosage of 20 to 80 grains (1.29 to 5.17 Gm.) daily. This treatment was continued for one week, after which the patients were completely recovered. Kato and Lane [191] reported a cure with sulfanilamide therapy, after two relapses, in a child of 6 years. Ahringsmann [192] treated 1 patient successfully with prontosil tablets (the original prontosil). Blumgart [193] reported 1 adult case in which the patient was cured with daily doses of 25 to 90 grains (1.62 to 5.82 Gm.) of sulfanilamide and collected 13 cases in the literature in which cure had been obtained with the drug or its derivatives. Several other cases have been reported in which recovery followed treatment with sulfanilamide, neoprontosil or both.

These drugs are apparently not effective in all cases. O'Reilly [194] had a failure with sulfanilamide in 1 case. Dalrymple-Champneys [195] had good results in only 10 of 17 cases with sulfanilamide and 2 of 15 cases with prontosil (probably the original prontosil). In 1 case in which he used prontosil soluble (neoprontosil) alone the result was good. In 2 cases both sulfanilamide and prontosil soluble were used, with a good result in 1 case but no effect in the other. It is, however, worth a thorough trial.

7. *Influenzal Meningitis.*—This infection has practically 100 per cent mortality. The use of serum has been followed by cure in only isolated cases. In most of these the patients have been adults. Folsom and Gerchow [196] reported a case of influenzal meningitis in a 10 year old boy treated successfully with sulfanilamide and prontosil solution (neo-

189. Traut, E. F., and Logan, C. E.: Undulant Fever Treated with Sulfanilamide, J. A. M. A. **111**:1092 (Sept. 17) 1938.

190. Stern, R. L., and Blake, K. W.: Undulant Fever: Its Treatment with Sulfanilamide, J. A. M. A. **110**:1550, (May 7) 1938.

191. Kato, D., and Lane, C. R.: Brucella Abortus Infection, Lancet **2**:77, 1937.

192. Ahringsmann, H.: Heilung der Bangschen Krankheit durch Prontosil, München. med. Wchnschr. **84**:1778, 1937.

193. Blumgart, H. L.: Sulfanilamide in Undulant Fever, J. A. M. A. **111**: 521 (Aug. 6) 1938.

194. O'Reilly, T. J.: Undulant Fever in a Sanatorium, Lancet **2**:430, 1938.

195. Dalrymple-Champneys, W.: The Prontosil Group in Br. Abortus Infections, Brit. M. J. **2**:471, 1938.

196. Folsom, T. G., and Gerchow, K. E.: Iufluenzal Meningitis Treated with Sulfanilamide, West Virginia M. J. **34**:254, 1938.

prontosil). Two patients with meningitis due to Friedländer's bacillus who were treated in the same manner died. Jones [197] reported 6 children suffering from this disease; the only child who received sulfanilamide was the only one who recovered. In this case ½ tablet was given twice a day from the second day of illness. Teggart [198] reported 1 recovery following the use of soluseptasine (disodium *p*- [γ-phenylpropylamino]-benzenesulfonamide-α-γ-disulfonate). Young and Moore [199] reported 1 recovery following treatment with anti-influenza serum and sulfanilamide. Taylor's [200] patient, a boy of 4 years treated orally and intrathecally with sulfanilamide, intramuscularly with prontosil (neoprontosil) and with serum, died. A patient reported on by Appelbaum [74] died. Of 18 patients treated by Neal [76] with sulfanilamide, prontosil (neoprontosil) and influenza serum, only 2 recovered. Of 5 patients reported on in a symposium on sulfanilamide, none recovered.[201] Povitsky [202] injected intraperitoneally into mice H. influenzae isolated from patients with meningitis and was able to protect from 4 to 6 of each series of 6 animals by the use of prontosil (neoprontosil) in combination with influenza serum. Neither alone offered any protection.

There is no evidence as yet that sulfanilamide is of value in the treatment of influenzal meningitis. Because of the high mortality of this disease, however, the drug should be given a thorough trial together with anti-influenza serum.

8. *Staphylococcic Infections.*—Results of chemotherapeutic treatment of staphylococcic infections have not been satisfactory. Marcus,[203] using sulfanilamide in doses of 1.5 to 2 Gm. daily for 62 patients, found it to be of no value against multiple lesions, such as impetigo, sycosis barbae, pustulous acne and multiple boils. But he found the drug to be effective when the infection was localized, as with a solitary boil or a furuncle of the nose. He observed that if the drug was given early, before necrosis occurred, boils, furuncles and whitlows usually healed in about three days and carbuncles in seven to ten days. Killmer and

197. Jones, H. W E.: H. Influenzae Meningitis, Brit. M. J. **2**:797, 1937.

198. Teggart, B.: Influenzal Meningitis Treated with Soluseptasine and Lumbar Puncture: Recovery, Brit. M. J. **1**:1365, 1938.

199. Young, R. H., and Moore, C.: Influenzal Meningitis Treated with Anti-Influenzal Serum and Sulfanilamide, Arch. Pediat. **55**:282, 1938.

200. Taylor, H.: Treatment of a Case of Influenzal Meningitis with Immune Serum and Sulfanilamide, Arch. Pediat. **55**:131, 1938.

201. Symposium on Sulfanilamide Therapy, J. Pediat. **11**:157, 1937.

202. Povitzky, O. R.: Immune Serum and Prontosil: Combined Treatment for Protection of the Mouse Against Fatal Dose of Haemophilus Influenzae Meningitis—Preliminary Report, New York State J. Med. **37**:1748, 1937.

203. Marcus, M.: Sulphanilamide in Staphylococcal Skin Infections, Brit. M. J. **2**:92, 1938.

Nehrkorn [204] treated nearly 50 patients who had infection of the skin, bones, joints and other regions with 3 to 6 tablets of uliron (dimethyldisulfanilamide) daily and with a 5 per cent salve of uliron applied locally. They found that the effect of the drug was favorable in staphylococcic infections but not as certain as that of prontosil (form not stated) in streptococcic infection. Six patients with staphylococcic-streptococcic ureterocystitis treated by Ajamil [205] showed improvement, but the urine did not become sterile in every case. Buskirk's [206] 4 year old patient, suffering from staphylococcic osteomyelitis of the jaw and septicemia, did not respond to prontosil (neoprontosil) and sulfanilamide. Durr [207] also experienced failure with sulfanilamide in treating an abscess of the lung with effusion and staphylococcic septicemia. Bloch and Pacella [208] reported staphylococcic meningitis in a 17 day old baby who recovered after intrathecal treatment with sulfanilamide for eight days and oral administration of 10 Gm. of sulfanilamide daily over a period of twenty-seven days. The spinal fluid culture was negative on the eleventh day. One patient with staphylococcic meningitis treated by Folsom and Gerchow [196] died, as did a patient with Staphylococcus aureus meningitis reported by Appelbaum.[74] Fenton and Hodgkiss [209] reported the recovery of a 35 year old patient from Staph. aureus septicemia after treatment with M & B 693 (sulfapyridine).

The experimental work of Mellon, Shinn and McBrown [210] in treating hemolytic Staph. aureus infections in mice indicated that disulfanilamide (sulfanilylsulfanilamide) was superior to either dimethyldisulfanilamide (D 373 Winthrop was used in these experiments) or sulfanilamide. However, their results in general were poor. They used disulfanilamide (sulfanilylsulfanilamide and diseptal (dimethyldisulfanilamide) in 4 cases of chronic staphylococcic osteomyelitis and the former in 1 case of acute staphylococcic arthritis, with

204. Killmer, G., and Nehrkorn, A.: Erfahrungen mit Uliron bei Staphylokokkeninfektionen, München. med. Wchnschr. **84**:2021, 1937.

205. Ajamil, L. F.: Staphylo-Streptococcic Uretero-Cystitis, and Its Treatment with Sulfanilamide, Urol. & Cutan. Rev. **41**:837, 1937.

206. Buskirk, R.: Osteomyelitis of the Jaw and Septicemia, Kentucky M. J. **36**:60, 1938.

207. Durr, S. P.: Lung Abscess with Effusion and Staphylococcus Septicemia, M. News Rock Island County **1**:12, 1938.

208. Bloch, H., and Pacella, B. L.: Staphylococcic Meningitis: Report of a Case in a Seventeen Day Old Infant Successfully Treated with Sulfanilamide, J. A. M. A. **110**:508 (Feb. 12) 1938.

209. Fenton, W. J., and Hodgkiss, F.: Staphylococcal Septicaemia Treated by M. & B. 693, Lancet **2**:667, 1938.

210. Mellon, R. R.; Shinn, L. E., and McBrown, J.: Therapy of Experimental Staphylococcus Infections with Sulfonamide Compounds, Proc. Soc. Exper. Biol. & Med. **37**:563, 1937.

poor results. The work of De and Basu [211] on mice infected with Staph. aureus was more promising. Treatment with staphylococcus antitoxin and antibacterial serum prolonged the life of 4 of 12 mice and protected 3 from death. Treatment with sulfanilamide prolonged the lives of 10 of 12 and protected 4 from death. A combination of both forms of treatment saved the lives of all the infected mice. By repeated doses of sulfanilamide Parish [212] was able to protect mice infected with virulent strains of staphylococci. He also found that the staphylococci persisted longer in the tissues of protected animals than streptococci and often gave rise to abscesses in the liver or spleen.

So far the reports on the use of sulfanilamide against staphylococcic infections have not been encouraging. Its use in large doses with staphylococcus toxoid or antitoxin in cases of severe infection should be given further trial.

9. *Abscess of the Brain.*—Sulfanilamide and neoprontosil have been used in the treatment of several patients who had abscess of the brain. Bucy [213] reported the case of a 4 year old girl who recovered with the use of sulfanilamide even after the meninges had been markedly soiled with hemolytic streptococcic pus from the abscess at the time of operation. Appelbaum [74] and Neal [76] each reported recovery in a patient with abscess of the brain due to hemolytic streptococcic infection. Neal [76] also reported failure in treating 4 patients with abscess of the brain; the infections were due, respectively, to a hemolytic streptococcus, B. influenzae, Staph. aureus and a mixture of organisms. Flake and Carey [75] reported on a 7 year old patient with mastoiditis and a large perisinal abscess with cultures positive for hemolytic streptococci who recovered when treated with sulfanilamide, prontosil soluble (neoprontosil) and surgical intervention. The successful treatment with prontosil (form not specified) and sulfanilamide of 2 patients with abscess of the brain was reported by Rowe.[214] One infection was pneumococcic and the other due to Friedländer's bacillus. Sulfanilamide is not regarded as effective against the latter type of infection. Both patients also had surgical therapy. Mellon and Bambas [215] also reported

211. De, S. P., and Basu, U. P.: Synergy in Experimental Chemotherapy of Staphylococcal Infections, Brit. M. J. **2**:564, 1938.

212. Parish, H. J., in discussion on Staphylococcal Infections in Man, Brit. M. J. **2**:335, 1937.

213. Bucy, P.: Sulfanilamide in the Treatment of Brain Abscess and Prevention of Meningitis, J. A. M. A. **111**:1639 (Oct. 29) 1938.

214. Rowe, S. N.: Use of Sulfanilamide in the Treatment of Brain Abscess, Ann. Surg. **107**:620, 1938.

215. Mellon, R. R., and Bambas, L. L.: Bacteriostatic Effect of Sulfanilamide in the Spinal Fluid of Convalescent Cases of Streptococcal Meningitis, Proc. Soc. Exper. Biol. & Med. **36**:682, 1937.

the recovery, on treatment with sulfanilamide and prontosil (neoprontosil), of a patient with an abscess of the brain from which the type V pneumococcus was cultured.

10. *Malaria.*—Both favorable and unfavorable reports are to be found concerning the value of sulfanilamide in the treatment of malaria. In experimental malaria in monkeys inoculated with Plasmodium knowlesi, Coggeshall [216] found that sulfanilamide was effective prophylactically and therapeutically. It had no effect, however, in avian malaria. Hill and Goodwin [217] reported 7 cases in which Plasmodium vivax malaria and 93 cases in which the Plasmodium falciparum type was cured with 10 cc. of prontosil (neoprontosil) given every twelve hours for four doses. There were no relapses. Two of the patients became reinfected but again responded to prontosil (neoprontosil). Van der Wielen [218] reported that in 2 patients who were receiving quartan malaria treatment for dementia paralytica the organisms disappeared from the blood and the malarial signs stopped after the administration of sulfanilamide. However, in 2 cases of tertian malaria resulting from mosquito bites and treated with the same drug he met with no success. Diaz de Leon,[219] on the other hand, reported 15 cases in which tertian malaria was treated with complete success with rubiazol (the original prontosil). He gave 2 tablets three times a day for four or five days and then 1 tablet three times a day. Fourteen of the patients had no further attacks. In 1 case a further attack was controlled by additional use of the drug. Faget, Palmer and Sherwood [220] and Mitchell [10] found sulfanilamide and prontosil soluble (neoprontosil) of no benefit in the treatment of malaria.

11. *Trachoma.*—The use of sulfanilamide in the treatment of trachoma holds considerable promise, if future reports bear out the results of present studies. In a recent excellent article Loe [221] reported his results in 140 patients with trachoma treated daily with 0.02 Gm. of sulfanilamide per pound of body weight for ten days and then with 0.016 Gm. per pound for fourteen days. His patients showed marked

216. Coggeshall, L. T.: Prophylactic and Therapeutic Effect of Sulfonamide Compounds in Experimental Malaria, Proc. Soc. Exper. Biol. & Med. **38**:768, 1938.

217. Hill, R. A., and Goodwin, M. H.: Prontosil in the Treatment of Malaria, South. M. J. **30**:1170, 1937.

218. van der Wielen, Y.: Prontosil in Quartan Malaria, Nederl. tijdschr. v. geneesk. **81**:2905, 1937.

219. Diaz de Leon, A.: Treatment of Malaria with Sulfonamide Compounds, Pub. Health Rep. **52**:1460, 1937.

220. Faget, G. H.; Palmer, M. R., and Sherwood, R. O.: Unsuccessful Treatment of Malaria with Sulfonamide Compounds, Pub. Health Rep. **53**:1364, 1938.

221. Loe, F.: Sulfanilamide Treatment of Trachoma, J. A. M. A. **111**:1371 (Oct. 8) 1938.

rapid improvement and cure. In the discussion of Loe's paper Gradle mentioned the good results he obtained in 25 cases.

12. *Gas Gangrene.*—Infections causing gas gangrene are becoming less uncommon because of the more frequent occurrence of crushing wounds and lacerations due to traffic and industrial accidents. Mitchell, Bryant and Chapman [222] in a recent review of the morbidity and mortality of gas gangrene in the state of New York, exclusive of New York city, reported that 208 patients had been hospitalized between 1932 and 1936. They stated the opinion that the diagnosis was certain in 135 cases. Infection by the group of spore-bearing bacteria causing this condition is probably as frequent as tetanus. The best treatment has included the use of polyvalent antitoxin, surgical débridement, irrigation of the wound with dilute solution of sodium hypochlorite and roentgen therapy. Recently Bohlman [223] reported on 3 patients (15, 21 and 42 years of age) with gas gangrene infection who had received 10,000 units of combined bacillary antitoxin which, however, had failed to prevent the development of the infection. All 3 patients were given sulfanilamide and recovered. The mortality with serum therapy is usually 53 per cent. He suggested that this drug may be specific for the gas bacillus or may act by checking symbiotic growth with the streptococcus. Kennedy [224] reported 1 case of gas gangrene successfully treated with serum, sulfanilamide, blood transfusions, roentgen therapy and surgical intervention. It is difficult to determine which treatment was responsible for the cure in this case. The work of Spray [225] indicates that the action of prontosil (neoprontosil), sulfanilamide and disulfanilamide (sulfanilylsulfanilamide) is selective against certain species of the anaerobic spore-bearing bacteria, notably Clostridium tetani, Clostridium lentoputrescens, Clostridium novyi, Clostridium septicum and Clostridium histolyticum. On the contrary, Clostridium welchii and the intensely proteolytic types, such as Clostridium sporogenes and Clostridium bifermentans as well as toxic Clostridium botulinum type A, are scarcely affected, at least by any concentration tolerated by human beings. He found that the bacteriostatic activity of the compounds increases progres-

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222. Mitchell, O. W. H.; Bryant, T. L., and Chapman, O. D.: Gas Gangrene: Morbidity and Mortality in New York State (Exclusive of New York City)—Based on General Hospital Reports for the Years 1932-1936 Inclusive, New York State J. Med. **38**:1022, 1938.

223. Bohlman, H. R.: Gas Gangrene Treated with Sulfanilamide, J. A. M. A. **109**:254 (July 24) 1937.

224. Kennedy, W. C.: Therapy of Gas Gangrene, with Report of a Case, Illinois M. J. **73**:260, 1938.

225. Spray, R. S.: Bacteriostatic Action of Prontosil Soluble, Sulfanilamide, and Disulfanilamide on Sporulating Anaerobes Commonly Causally Associated with Gaseous Gangrene, J. Lab. & Clin. Med. **23**:609, 1938.

sively in the order of prontosil (neoprontosil), sulfanilamide and disulfanilamide (sulfanilylsulfanilamide). In view of Bohlman's success in the 3 cases mentioned, Spray suggested that there is possibly some secondary therapeutic activity of the drug other than direct bacteriostatic action. By using sulfanilamide Long and Bliss [226] were able to protect mice infected intraperitoneally with Cl. welchii.

13. *Chancroid (Ducrey's Bacillus).*—Kornblith, Jacoby and Wishengrad [227] reported a series of 45 cases of chancroid diagnosed through clinical signs and confirmed by positive smears for Ducrey bacilli as well as by positive cutaneous reactions with the Ducrey antigen. The lesions varied between an ulcer the size of a dime and ulceration of the entire glans. The average duration was from four weeks to two years. Treatment consisted of giving 80 grains (5.18 Gm.) of sulfanilamide daily for the first five days and 40 grains (2.59 Gm.) for an additional nine days. All lesions treated in this fashion healed promptly by the end of the two weeks, with no recurrences. Hanschell [228] reported cures in 20 cases of chancroid treated with injections of prontosil soluble (neoprontosil), 5 per cent solution, and with sulfanilamide given by mouth. Complete healing occurred in from five to ten days. Batchelor and Lees [229] reported 10 cases in which the patients were rapidly cured. Thirty-five patients with bubo, some with a concomitant chancroid on the penis, were treated by Hutchison.[230] The average period for cure with sulfanilamide was fifteen and one-half days, as compared with forty-six and one-half days for patients treated with "Dmelcos" vaccine (a stabilized suspension of Ducrey bacilli) or local applications.

Sulfanilamide is proving to be the best therapeutic agent in the treatment of chancroid.

14. *Venereal Lymphogranuloma.*—This disease has been refractory to most forms of therapy. The recent reports of sulfanilamide therapy are fairly encouraging. Of Shropshear's [231] 9 patients with stricture of

226. Long, P. H., and Bliss, E. A.: Observations upon the Experimental and Clinical Use of Sulphanilamide in the Treatment of Certain Infections, Canad. M. A. J. **37**:457, 1937.

227. Kornblith, B. A.; Jacoby, A., and Wishengrad, M.: Treatment of Chancroid with Sulfanilamide, J. A. M. A. **111**:523 (Aug. 6) 1938.

228. Hanschell, H. M.: Sulphanilamide in the Treatment of Chancroid, Lancet **1**:886, 1938.

229. Batchelor, R. C. L., and Lees, R.: Treatment of Chancroid with Sulphanilamide, Brit. M. J. **1**:1100, 1938.

230. Hutchison, A.: Treatment of Bubo with Sulphanilamide, Lancet **1**:1047, 1938.

231. Shropshear, G.: Sulfanilamide in the Treatment of Strictures of the Rectum Caused by Lymphogranuloma Venereum, Illinois M. J. **74**:153, 1938.

the rectum caused by lymphogranuloma venereum, 8 were given 30 grains (1.8 Gm.) of sulfanilamide daily for fifteen days and 1, the same total over twenty-three days. This was repeated after a rest of seven to ten days. The total dose ranged between 54 and 108 Gm. There was gradual to rapid response in all 9 cases. In 3 males with inguinal adenitis and in 1 female with chronic vulvar ulcers improvement occurred but not a complete cure. Kubitski [113] reported good results in 2 cases of venereal lymphogranuloma with the use of prontosil (neoprontosil) and prontosil tablets (the original prontosil). Phylactos [232] reported a cure with intramuscular injection of prontosil (the original prontosil). Levaditi [233] found sulfanilamide effective in preventing and curing the infection produced by inoculating guinea pigs with the virus of venereal lymphogranuloma, while Bär [234] found that the drug retarded the course of the disease but cure was exceptional in experimentally infected mice.

Sulfanilamide should be given a thorough trial in cases of lymphogranuloma venereum.

15. *Miscellaneous Infections.*—Erythema Multiforme and Erythema Nodosum: Szentkiralyi [235] found sulfanilamide effective in these conditions.

Actinomycosis: Walker [236] reported the cure of 1 patient with actinomycosis, 1 Gm. of sulfanilamide being given three times a day for seven days and again for five days after a ten day interval. Poulton [237] reported that sulfanilamide cured abdominal actinomycosis in 1 case.

Although there has been insufficient clinical trial in cases of actinomycosis, sulfanilamide holds promise of being the best therapeutic agent thus far available.

Typhoid and Paratyphoid Infections: There is much need of further clinical study on the effects of sulfanilamide therapy. A few isolated reports have appeared in the literature, but these are too few for one to judge from them. Barer [184] reported a cure with sulfanilamide in 1 case of persistent typhoid bacilluria and pyelitis. Bazin [239] successfully

232. Phylactos: Sun un cas de maladie de Nicolas-Fevre, guérie par le 4-sulfonamide-2,4-diaminoazobenzol, Presse méd. **46**:1153, 1938.

233. Levaditi, C.: Chimiothérapie de la lymphogranulomatose inguinale expérimentale, Compt. rend. Soc. de biol. **128**:138, 1938.

234. Bär, F.: Chemotherapeutische Versuche bei der experimentellen Infektion der Maus mit Lymphogranuloma inguinale, Klin. Wchnschr. **17**:588, 1938.

235. Szentkiralyi, Z.: Treatment of Erythema Exudativum (Multiforme) and Erythema Nodosum with Deseptyl (Sulfanilamide), Orvosi hetil. **81**:794, 1937.

236. Walker, O.: Sulphanilamide in the Treatment of Actinomycosis, Lancet **1**:1219, 1938.

237. Poulton, E. P., in discussion on Treatment of Bacterial Diseases with Sulphanilamide and Its Congeners, Brit. M. J. **2**:929, 1937.

238. Footnote deleted.

treated with sulfanilamide a carrier of paratyphoid organisms. There was heavy infection of the hepatic bile, as demonstrated by culture of paratyphoid bacilli after cholecystectomy. In mice experimentally infected with typhoid and paratyphoid organisms Buttle and co-workers [240] found sulfanilamide to be effective.

Bubonic Plague (Bacillus Pestis, Oriental Plague): Carman [240a] treated 6 patients who had bubonic plague with prontosil (neoprontosil). Three of these recovered. Nine controls seen at the same time died. Carman used 2.5 to 5 cc. of prontosil twice daily.

Pemphigus: Up to the present the treatment has been thoroughly unsatisfactory, and the prognosis has usually been hopeless. Caro [241] reported 2 cases; in 1 a diabetic patient treated with 0.3 Gm. of sulfanilamide four times a day showed marked improvement over one month; the other patient was given 0.6 Gm. of sulfanilamide six times a day, 15 grains (0.97 Gm.) of sodium bicarbonate being administered with each dose. The dose of sulfanilamide was reduced to 0.3 Gm., given five times a day. At the end of the first week there were no new lesions, and the old lesions were rapidly healing at the time of the report.

Lain and Lamb [242] reported 1 case of a pemphigoid eruption from which the patient spectacularly recovered after sulfanilamide therapy.

Lupus Erythematosus: Linser [243] reported on 3 patients successfully treated with prontosil (the original prontosil). Of 5 patients treated by Ingels [244] with sulfanilamide there was complete clearing in 2 and improvement in the other 3.

Chronic Ulcerative Colitis: Bannick, Brown and Foster [54] treated 9 patients with this condition and obtained improvement, generally marked and rapid, in all of them. Both neoprontosil, in 5 grain tablets or in capsules, and sulfanilamide were used orally. As yet far too few reports are available for one to estimate the value of these drugs against colitis.

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239. Bazin, A. T.: A Paratyphoid B Carrier Successfully Treated with Sulphanilamide, Canad. M. A. J. **38**:559, 1938.

240. Buttle, G. A. H.; Parish, H. J.; McLeod, M., and Stephenson, D.: The Chemotherapy of Typhoid and Some Other Non-Streptococcal Infections in Mice, Lancet **1**:681, 1937.

240a. Carman, J. A.: Prontosil in the Treatment of Oriental Plague, East African M. J. **14**:362, 1938.

241. Caro, M. R.: Pemphigus: Treatment with Sulfanilamide; Preliminary Report, Arch. Dermat. & Syph. **37**:196 (Feb.) 1938.

242. Lain, E. S., and Lamb, J. H.: Treatment of Pemphigoid Eruption with Sulfanilamide: Report of a Case, Arch. Dermat. & Syph. **37**:840 (May) 1938.

243. Linser, K.: Heilung von Lupus erythematodes durch Prontosilbehandlung, Dermat. Wchnschr. **106**:342, 1938.

244. Ingels, A. E.: Lupus Erythematosus Treated with Sulfanilamide, Arch. Dermat. & Syph. **37**:879 (May) 1938.

Osteomyelitis: As rapid or as good therapeutic results cannot be expected with infections of bones because of the decreased blood supply and fluid content of these tissues. Weidekamp,[245] however, treated 64 patients who had osteomyelitis, usually with a mixed infection, and tuberculosis with prontosil (the original prontosil) given orally and obtained marked improvement in 26. Good results were reported by Smith,[66b] who treated 2 patients with hemolytic streptococcic arthritis of the hip joint with prontosil soluble (neoprontosil) and sulfanilamide. Shapiro and Morris[247] treated pneumococcic osteomyelitis and polyarthritis secondary to scorbutic hemorrhages in a 9 month old infant; they used pneumococcus serum and sulfanilamide, with recovery of the patient.

Other Infections: There are a few reports on the satisfactory results obtained with sulfanilamide and its derivatives in cases of pyephlebitis and abscess of the liver as well as of peritonitis as a complicating appendicitis.

Canine distemper, a virus disease, has been successfully treated by Marcus and Necheles[248] with sulfanilamide or prontosil (neoprontosil) and by Larsen[249] with sodium sulfanilylsulfanilate (N′-1[phenyl-4-sodium sulfonate]-paraaminobenzenesulfonamide). The dosage of sulfanilamide was 0.33 Gm. given orally three times a day and 100 cc. of a 1 per cent solution given subcutaneously twice a day; 1 cc. of neoprontosil per kilogram was given twice a day. The dose of sodium sulfanilylsulfanilate was 15 grains (0.96 Gm.) given daily for three days. Dochez and Slanetz[250] used the latter drug prophylactically against canine distemper with success. However, Plummer, Mitchell and Walker[251] were unable to protect or successfully treat ferrets infected with distemper virus.

PROPHYLACTIC EFFECT OF SULFANILAMIDE

So far no convincing evidence has been presented that sulfanilamide has a prophylactic value in preventing diseases or infections in human

245. Weidekamp, M.: Zur Behandlung der mischinfizierten Knochentuberkulose und der Osteomyelitis mit Prontosil, Deutsche med. Wchnschr. **64**:854, 1938.

246. Footnote deleted.

247. Shapiro, E., and Morris, M.: Scorbutic Subperiosteal Hemorrhage Complicated by Osteomyelitis and Pyoarthrosis, Arch. Pediat. **55**:465, 1938.

248. Marcus, P. M., and Necheles, H.: Treatment of Spontaneous Canine Distemper with Sulfanilamide, Proc. Soc. Exper. Biol. & Med. **38**:385, 1938.

249. Larsen, C. E.: Sodium Sulfanilyl Sulfanilate in Canine Distemper, J. Am. Vet. M. A. **46**:197, 1938.

250. Dochez, A. R., and Slanetz, C. A.: Treatment of Canine Distemper with a Chemotherapeutic Agent, Sodium Sulfanilyl Sulfanilate, Science **87**:142, 1938.

251. Plummer, P. J. G.; Mitchell, C. A., and Walker, R. V. L.: Experiments with Sodium Sulfanilyl Sulfanilate, Canad. J. Comp. Med. **2**:139, 1938.

beings. During an epidemic of infections of the throat, Smith [66b] found sulfanilamide and parabenzylaminobenzenesulfonamide of no prophylactic value, although they were effective after the infection was acquired. Similarly, it has been used with little or no proved success in preventing obstetric infections, scarlet fever and meningitis.

DISEASES NOT AFFECTED BY SULFANILAMIDE OR ITS DERIVATIVES

Experimental and clinical investigations have failed to show any noticeable effect of sulfanilamide or its derivatives in the following diseases: rheumatic fever, infectious and rheumatoid arthritis, tularemia, tuberculosis, Hodgkin's disease, periarteritis nodosa, thromboangiitis obliterans, infected pulmonary embolus, poliomyelitis, trichiniasis, pertussis, syphilis,[229] influenza, infection with Friedländer's bacillus, bacillary dysentery and certain virus diseases of both human beings and animals.

Rheumatic Fever.—Swifth, Moen and Hirst [252] treated 8 selected and well controlled patients who had rheumatic fever. They found that sulfanilamide had little if any detectable beneficial effect on the course of the disease, once the condition was well established. Often the toxic effects of the drug intensified the rheumatic manifestations. They therefore did not advise its use. Massell's [253] investigation from a prophylactic point of view is also of interest, although his series is small. Because of the well known frequence with which recrudescences of rheumatic fever follow infections of the upper respiratory tract, the prophylactic effect of sulfanilamide was studied. Six patients with rheumatic fever who had infections of the upper respiratory tract and material from whose throats yielded hemolytic streptococci on culture were given the drug. Six similar patients observed as controls were given acetylsalicylic acid instead. Two patients of each group had recrudescences of rheumatic fever, and 1 of each group died. The course of the throat infections was similar in the two groups. Those receiving acetylsalicylic acid were the more comfortable. Massell treated with sulfanilamide 2 patients suffering from active chorea and 2 with acute rheumatic fever, obtaining no favorable results. In a later paper Massell and Jones [254] reported no beneficial effect of sulfanilamide in 58 cases of rheumatic fever, in 7 of which chorea was present.

252. Swift, H. F.; Moen, J. K., and Hirst, G. K.: The Action of Sulfanilamide in Rheumatic Fever, J. A. M. A. **110**:426 (Feb. 5) 1938.

253. Massell, B. F.: Studies on the Use of Prontylin in Rheumatic Fever, New England J. Med. **216**:487, 1937.

254. Massell, B. F., and Jones, T. D.: Effect of Sulfanilamide on Rheumatic Fever and Chorea, New England J. Med. **218**:876, 1938.

Tuberculosis.—Rich and Follis [255] found that in guinea pigs with experimental tuberculosis treated with sulfanilamide the macroscopic and microscopic evidence of the disease was significantly less than in the untreated controls. Smithburn [256] found the drug ineffective in experimental tuberculosis. Marcou,[257] although he found the sulfonamides to have no effect on infections with Koch's bacillus, recommended its use against mixed suppurative infections which are tuberculous as well as streptococcic and staphylococcic. Weidekamp [245] found that in 64 cases of mixed infections with tuberculosis of the bone prontosil tablets (the original prontosil) were of value.

Trichiniasis.—McCoy [258] reported sulfanilamide to be ineffective in the treatment of trichiniasis in rats.

Poliomyelitis.—Toomey and Takacs [259] were unable to prevent or to modify the occurrence of poliomyelitis in monkeys through the use of sulfanilamide. Similar failures with experimental poliomyelitis in monkeys were reported by Rhodes and Rooyen,[260] with the use of prontosil (form not specified), and by Kelson [261] and McKinley, Acree and Meek [262] with the use of sulfanilamide.

Pertussis.—Gross, Cooper and Lewis [263] treated mice inoculated with virulent pertussis bacilli with sulfanilamide, 4,4′-di-(acetylamino)-diphenylsulfone and 4,4′-diaminobenzenesulfonanilide; they observed no beneficial effect. Cruickshank [264] made similar observations with sulfanilamide and 2-(paraaminobenzenesulfonamido)-pyridine (sulfapyridine).

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255. Rich, A. R., and Follis, R. H.: Inhibitory Effect of Sulfanilamide on the Development of Experimental Tuberculosis in Guinea Pigs, Bull. Johns Hopkins Hosp. **62**:77, 1938.

256. Smithburn, K. C.: Inefficacy of Sulfanilamide in Experimental Tuberculosis, Proc. Soc. Exper. Biol. & Med. **38**:574, 1938.

257. Marcou: Traitement de la tuberculose par les sulfamidés, Presse méd. **46**:421, 1938.

258. McCoy, O. R.: Ineffectiveness of Sulfanilamide in Treatment of Trichiniasis in Rats, Proc. Soc. Exper. Biol. & Med. **38**:461, 1938.

259. Toomey, J. A., and Takacs, W. S.: Merphenyl Borate and Sulfanilamide in Experimental Poliomyelitis, Arch. Pediat. **55**:307, 1938.

260. Rhodes, A. J., and van Rooyen, C. E.: Chemotherapy of Virus Diseases, Brit. M. J. **1**:924, 1938.

261. Kelson, S. R.: Use of Sulfanilamide in Experimental Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **36**:718, 1937.

262. McKinley, E. B.; Acree, E. G., and Meek, J. S.: Sulfanilamide and Virus Disease, Science **87**:43, 1938.

263. Gross, P.; Cooper, F. B., and Lewis, M.: Chemotherapy of B. Pertussis Infections of Mice, Proc. Soc. Exper. Biol. & Med. **38**:407, 1938.

264. Cruickshank, J. C.: Sulphanilamide and "M. & B. 693" in Experimental Pertussis in Mice, Lancet **2**:310, 1938.

MISCELLANEOUS VIRUS DISEASES

Choriomeningitis.—In mice experimentally infected with the virus of this disease Levaditi [265] was unable to demonstrate any therapeutic effect with sulfanilamide, with the original prontosil and with several derivatives. In contrast, Rosenthal, Wooley and Bauer [266] found that prontosil (the original prontosil) had some protective action in mice but that prontosil soluble (neoprontosil), sulfanilamide and disulfanilamide (sulfanilylsulfanilamide) did not.

Equine and American Encephalitis.—Plummer, Mitchell and Walker,[251] using sodium sulfanilylsulfanilate, failed to obtain a therapeutic effect in treating guinea pigs infected with equine encephalitis virus. Neoprontosil, sulfanilamide, disulfanilamide and the original prontosil were found by Rosenthal, Wooley and Bauer [266] to be inactive against the St. Louis encephalitis virus. Levaditi [265] found sulfanilamide, the original prontosil and other related compounds not effective in treating guinea pigs infected with American encephalitis.

Influenza.—Oakley,[267] Rosenthal and his co-workers [266] and Levaditi [265] found sulfanilamide and several related compounds, such as the original prontosil, neoprontosil, disulfanilamide (sulfanilylsulfanilamide) and sodium sulfanilylsulfanilate, ineffective in treating mice infected intranasally with influenza virus. Climenko, Crossley and Northey [268] reported that some sulfanilamide compounds but not sulfanilamide or sodium sulfanilylsulfanilate are capable of protecting mice against experimental influenzal infections (intranasal). Hunter [269] reported that 4 patients who had "influenza" with streptococcic infection were all successfully treated with prontosil (neoprontosil). Of these 1 was moribund at the time of treatment. Martini [270] suggested that the sulfonamide compounds may prove of value in the treatment of influenza, especially if mixed infection is present.

265. Levaditi, C.: L'activité thérapeutique des dérivés benzéniques sulfurés dans les maladies provoquées par les ultravirus, Compt. rend. Soc. de biol. **127**: 958, 1938.

266. Rosenthal, S. M.; Wooley, J. G., and Bauer, H.: Studies on Chemotherapy, Pub. Health Rep. **52**:1211, 1937.

267. Oakley, C. L.: Chemotherapy of Virus Infections, Brit. M. J. **1**:895, 1938.

268. Climenko, D. R.; Crossley, M. L., and Northey, E. H.: The Protective Action of Certain Sulfanilamide Derivatives in Experimental Influenza Infections, J. A. M. A. **110**:2099 (June 18) 1938.

269. Hunter, F. J.: Influenza with Streptococcal Infection, M. Rec. **145**:387, 1937.

270. Martini, P.: Die Therapie der Grippe, München. med. Wchnschr. **84**:1848, 1937.

RELATION TO IMMUNOLOGIC RESPONSE

The question of the relation of sulfanilamide to the immunologic response of the patient to infections should also be mentioned here, as well as the possibility that organisms will become resistant to the drug after once showing an apparent response. It seems unlikely that sulfanilamide hinders the production of immunity in the patient, so that similar future or recurrent infections will become more serious, any more than that the immunologic response is changed by immune serum. Whether bacteria can become resistant to sulfanilamide after at first being apparently susceptible is a different matter. So far there has been nothing in the literature in regard to this. In our own experience we have questioned at times whether or not one or both of these factors was not responsible for the recurrence of some otitic infections. We have seen both otitis media and mastoiditis apparently subside and then, after a week or more, recur again with an apparently more serious infection. At times this recurrence would again subside on use of the drug, but more often it would respond not at all or at least not as readily as it did the first time. These recurrences took place in spite of what appeared to be adequate sulfanilamide therapy, with continuation of therapy for several days after the original infection had apparently subsided. In some experimental work that has been reported in which animals were inoculated with bacteria and then treated with sulfanilamide, the animals that survived often presented abscesses some time after therapy was discontinued, apparently from organisms that had been lying dormant.

Although the possibilities just mentioned are present, we believe that they should not militate against the use of sulfanilamide; according to our present knowledge, the advantages of its use, when it is indicated, far outweigh any disadvantages.

SUMMARY

We have attempted to present as clear and complete a review of the material on sulfanilamide, gathered from the literature and from our own experience, as has seemed practicable. It would be impracticable to include all references in the literature. Particular emphasis has been laid on the range and limitation of application of the medicament and on what has been found to be the optimal dosage and mode of administration with the different diseases. Sulfanilamide has proved to be one of the most effective drugs in the treatment of certain diseases. It is safe to predict that in the future many new derivatives and compounds of sulfanilamide will be added to the therapeutic armamentarium.

It has been our purpose to define the fields of usefulness of the drug, and in the discussion of its toxicity and reactions we have tried to show not only its dangers but also its innocuousness when it is used intelligently. As inadequate dosage has invariably led to failure, we hope

that this paper will provide a greater degree of assurance to physicians who have hesitated to use this drug in amounts sufficient to be of value. On the other hand, we hope that this review will generate in the minds of the readers as great a respect for the dangers of sulfanilamide as for its usefulness. With the rapid introduction to the medical profession of new preparations and derivatives, the warning of the American Medical Association's Council on Pharmacy and Chemistry should be emphasized. The preparations which have not been investigated by the Council or on which experimental studies are insufficient should not be used. Such preparations as sulfanilylsulfanilamide (disulfanilamide) and dimethyldisulfanilamide are still in the experimental stage, as far as general medical practice is concerned.

707 Fullerton Avenue.

News and Comment

GENERAL

Study of Obstetric Difficulties After Infantile Paralysis.—Dr. Samuel Kleinberg and Dr. M. T. Horwitz are conducting an investigation of the obstetric difficulties of patients who have had infantile paralysis. This study is being pursued at the Hospital for Joint Diseases under a grant from the National Foundation for Infantile Paralysis. Should you know of any such cases, please communicate with Dr. Kleinberg or Dr. Horwitz, care of the research department, Hospital for Joint Diseases, 123d Street and Madison Avenue, New York.

American Board of Pediatrics.—The American Board of Pediatrics will hold examinations on November 14 and 15, in Cincinnati, preceding the annual meeting of the American Academy of Pediatrics. Appointments for this examination must be made before July 14, 1939.

UNIVERSITY NEWS

Columbia University.—Dr. A. A. Weech has been appointed director of the Normal Child Development Study at Columbia University, replacing Dr. Herbert D. Wilcox, who has become director of the New York Academy of Medicine.

CORRECTION

In the article by Drs. Andrew W. Brown and I. P. Bronstein and Ruth Kraines, entitled "Hypothyroidism and Cretinism in Childhood: VI. Influence of Thyroid Therapy on Mental Growth," which appeared in the March 1939 issue (Am. J. Dis. Child. **57**:517, 1939), the date of the meeting of the American Psychological Association, Minneapolis, on page 517, should read September 1937 instead of 1938.

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

Study of Hemolytic Streptococci with Reference to the Correlation Between Their Group Specific Substances and Biochemical Characteristics. M. D. Hechler and M. A. Farrell, J. Infect. Dis. **63**:225 (Nov.-Dec.) 1938.

A study of the serologic and biochemical properties of 42 strains of hemolytic streptococci led to the following conclusions: By precipitin tests 37 of the 42 strains belong to the seven serologic groups of Lancefield. Five of the seven serologic groups show in a large majority of cases a definite relation to the source of the strains.

The biochemical and cultural characteristics of all strains within a group are somewhat variable, although predominant group reactions are noted. Certain correlations are indicated between the group-specific substances and fermentative reactions.

Toomey, Cleveland.

Viability of Pneumococci in Dried Sputum. E. G. Stillman, J. Infect. Dis. **63**:340 (Nov.-Dec.) 1938.

Stillman reports that pneumococci were recovered from dried sputum which had been exposed to diffuse daylight at room temperature for months and that pneumococci lived in dried sputum stored in the cold on an average four or five times longer than when the factor of cold was omitted.

Toomey, Cleveland.

Failure of Bacteria Other Than Staphylococci to Produce Enterotoxic Substance. F. R. Hunter and G. M. Dack, J. Infect. Dis. **63**:346 (Nov.-Dec.) 1938.

Filtrates were prepared from cultures of twelve different kinds of bacteria, i. e., Bacterium coli, Proteus, Salmonella, Bacterium cloacae and streptococci of the alpha type, which were grown in mediums prepared with and without starch. The filtrate from a culture on medium containing starch and the corresponding control filtrate from a culture on medium containing no starch were fed in triplicate to monkeys. These animals were observed continuously for a period of five hours and at intervals of eight, twelve and twenty-four hours after feeding. No symptoms of food poisoning were observed. At the conclusion of these experiments, similarly prepared filtrates from cultures of a strain of Staphylococcus known to be responsible for food poisoning were fed, and 4 of the 6 animals vomited and showed typical symptoms of food poisoning. These results are not in agreement with those of Jordan and Burrows, who reported that many organisms other than food poisoning staphylococci could produce enterotoxic substance if grown under certain conditions on medium containing starch.

Toomey, Cleveland.

Metabolism; Infant Feeding; Milk and Other Foods

Dietary Protein and the Regeneration of Serum Albumin: I. Method of Assay and Discussion of Principles. A. A. Weech and E. Goettsch, Bull. Johns Hopkins Hosp. **63**:154 (Sept.) 1938.

A method is described for assaying food proteins with respect to their potency in promoting the formation of serum albumin: A basal low protein diet is fed to dogs, causing depletion in their serum albumin. The test food is then added to

the diet, and the rise in albumin during a standard period is measured. The average of the values from a number of such assays, on different animals, gives the potency of the test food. The results of a dozen assays of casein are presented to illustrate the type of data yielded by the method.

Measurements of plasma volume, analyzed to show the relationship between the concentration of albumin and the circulating quantity of albumin, do not improve the consistency of the results.

An analysis of the behavior of the globulin fraction fails to show that diet is an important factor in influencing the formation of globulin.

The nature of the stimulus for regeneration of serum albumin is discussed. When the body mechanism for forming the protein is normal, the course of regeneration on a constant diet can be represented by a straight line until the level of health is regained. No support was found for the assumption that the intensity of the stimulus is proportional to the degree of depletion. After prolonged depletion of body protein, the course of the regeneration curve may be altered. Under such circumstances initial regeneration is rapid until a subnormal level is reached; subsequent regeneration is extremely slow and appears to depend not on diet but on the time required for restoration of the organ concerned in synthesizing albumin to normal. Similar circumstances in human disease may limit the effectiveness of diets composed of foods of high potency.

A statistical analysis of the errors involved in making the assays is presented.

FROM AUTHORS' SUMMARY, New York.

DIETARY PROTEIN AND THE REGENERATION OF SERUM ALBUMIN: II. COMPARISON OF THE POTENCY VALUES OF BEEF SERUM, BEEF MUSCLE AND CASEIN. A. A. WEECH and E. GOETTSCH, Bull. Johns Hopkins Hosp. **63**:181 (Sept.) 1938.

The values obtained in eleven assays of beef serum, twelve assays of beef muscle and twelve assays of casein for potency in forming serum albumin are compared. The values are: beef serum, 0.801; beef muscle, 0.475; casein, 0.388. The difference between beef serum and beef muscle and between beef serum and casein are highly significant; the difference between beef muscle and casein is not significant.

The order of potency for the three foods is the same as that calculated from data previously reported by Whipple and collaborators.

FROM AUTHORS' SUMMARY.

A SIMPLE METHOD OF PRESERVING BREAST MILK. M. J. WILMERS, Proc. Roy. Soc. Med. **31**:759 (May) 1938.

Wilmers describes a simple method of preserving breast milk. The milk can be kept indefinitely in a refrigerator. The method was first used in a hospital for infants in June 1937. A total of 103 pints was bottled during a period of six months. The preserved milk was fed to 30 infants without any untoward results. Three samples of milk kept, respectively, three weeks, six weeks and two months were examined bacteriologically. They were all satisfactory, 10 cc. of each sample breeding a scanty growth of white staphylococci and 1 cc., 0.1 cc. and 0.01 cc. being sterile.

WILLIAMSON, New Orleans.

STAPHYLOCOCCUS ANTITOXIN IN COLOSTRUM, IN HUMAN MILK AND IN COW'S MILK. R. SCAPATICCI, Lattante **9**:363 (Sept.) 1938.

The content of staphylococcus antitoxin per cubic centimeter is the same in the milk as in the blood serum of the mother. The staphylococcus antitoxin in the colostrum, however, is greater than that in the blood serum. Staphylococcus antitoxin is present in cow's milk, but data as to the relative amounts in the milk and blood serum of any given cow are not given.

HIGGINS, Boston.

PATHOLOGY OF SODIUM CHLORIDE METABOLISM (DIABETES INSIPIDUS OCCULTUS). G. FANCONI, Riv. di clin. pediat. **36**:708 (Aug.) 1938.

Normal children whose blood plasma shows sodium chloride varying between 340 and 365 mg. per hundred cubic centimeter are in a state of chlorostability. The body will maintain this chloride level quite constant in spite of marked variations in the chloride and water intake. When this regulation of the level of chloride is damaged, however, the organism becomes more or less chlorolabile and may in consequence show marked symptoms.

The symptoms of lack of sodium chloride are seen in marked extrarenal loss of sodium chloride, as in diarrhea and vomiting, in certain abnormalities of renal function and in acidosis, as in diabetes, in giving too much dextrose intravenously and in poor function of the adrenals, as in Addison's disease. The symptoms of the retention of sodium chloride are seen in renal insufficiency with edema and in alterations of the hypophysial-diencephalic centers, as in diabetes insipidus.

Several case reports are given, demonstrating abnormalities of chloride metabolism as seen in children. In case 1, a hydrocephalic child was intentionally given large amounts of sodium chloride in the hope of diminishing the size of the head. When 5 Gm. of sodium chloride was given daily by mouth, the chloride in the urine increased to 1.16 per cent, three times the existing normal chloride content of the blood. When the dose of sodium chloride was increased to 10 Gm. per day, the chloride in the blood increased to 446 mg. per hundred cubic centimeters, and hyperpyrexia followed, with the temperature mounting to 41 C. (105.8 F.). The chloride intake was reduced, and within twenty-four hours the fever disappeared.

The second case was that of a boy of 2 years with diabetes insipidus. When the fluid intake was restricted, the temperature rose, and when fluid was again allowed in large amounts the temperature fell. The child was chlorolabile, the chloride content of the blood being 461 mg., rising to 495 mg. on restriction of the fluid intake.

The third child had diabetes insipidus occultus, ordinarily having neither polyuria nor polydipsia. He was, however, chlorolabile, the concentration of chloride in the serum being from 446 to 460 mg. per hundred cubic centimeters. This child could not excrete more than 0.2 per cent chloride in the urine, but his sweat showed a chloride concentration of 1.1 per cent; the normal content of perspiration is between 0.03 and 0.2 per cent.

A fourth child, with a tumor in the hypothalamic region, also showed a high level of chloride in the serum; he was chlorolabile at times, having diabetes insipidus occultus.

HIGGINS, Boston.

BACTERIA IN DRIED, CONDENSED AND EVAPORATED MILKS. J. M. TURNBULL, Rev. mex. de puericultura **8**:139 (Feb.) 1938.

At times it is necessary to use evaporated, condensed or dried milk in infant feeding. These milks should be sterile. Evaporated, unsweetened milk has proved to be the best. It was always found sterile, whereas the others were not always so found.

HERRON, Monroe, La.

Acute Contagious Diseases

THE PRESENT STATUS OF METHODS FOR THE PROPHYLAXIS OF ACUTE ANTERIOR POLIOMYELITIS. J. A. KOLMER, Ann. Int. Med. **12**:95 (July) 1938.

Experimental studies show that the virus of poliomyelitis is absorbed by way of the olfactory nerves, but evidence is available suggesting that other portals of entry of the virus may be the oropharyngeal mucosa, tonsils, trachea and even the intestinal tract. Therefore it is not logical to expect that chemotherapeutic agents applied to the olfactory bulbs will be successful in conferring immunity in any appreciable number of instances.

The opinion is expressed that the intramuscular injection of from 20 to 40 cc. of normal or convalescent serum known to contain antibody, on the basis of neutralization tests with monkey serum, is still a hopeful prophylactic measure for children. A practical test for determining individual susceptibility to poliomyelitis is urgently required.

READING, Galveston, Texas.

PROPHYLAXIS OF THE COMMON COMMUNICABLE DISEASES OF CHILDHOOD. F. H. TOP, Arch. Pediat. **55**:259 (May) 1938.

The methods of active and passive immunization against the common communicable diseases are reviewed.

ORR, Buffalo.

ACUTE ANTERIOR POLIOMYELITIS: PART II. H. H. HYLAND, W. J. GARDINER, F. C. HEAL, W. A. OILLE and O. M. SOLANDT, Canad. M. A. J. **39**:105 (Aug.) 1938.

In this series of 66 adult patients 16 were placed in the respirator; 10 of the latter group had bulbar involvement as well as paralysis of respiratory muscles; 7 died soon after being placed in the respirator; the remaining 9, including 4 with bulbospinal disease, were alive approximately six months after the onset of their illness; 5 were still receiving respirator treatment.

Estimations of vital capacity were made on some of the patients and were found to be accurate indexes of improvement.

Not only was it found that the respiration kept the patient alive during the acute stage; it was found that it permitted rest and passive movement. There was evidence that periodic increases in negative pressure in the respirator, by increasing the tidal air far above the resting level, could move the ribs. This is important, as the costovertebral articulations tend to stiffen if immobilized by intercostal paralysis.

In their summary the authors note that in a series of serum-treated patients and controls the incidence of paralysis and the incidence of deaths were not essentially different in the group receiving serum in the preparalytic stage and the group not receiving serum. In the group without respiratory difficulties it was found that early and continued controlled exercises were important. Even during the preliminary splinting stage passive motion was found desirable. Thus the authors stress the importance of early reeducation of the muscles.

MOORE, Omaha.

CHANGES IN THE OLFACTORY MUCOSA AND THE OLFACTORY NERVES FOLLOWING INTRANASAL TREATMENT WITH ONE PER CENT ZINC SULPHATE. C. G. SMITH, Canad. M. A. J. **39**:138 (Aug.) 1938.

Experiments were carried out on rats to determine the effects of zinc sulfate solution used as a prophylactic agent in an epidemic of poliomyelitis. The experiments showed that three types of cells in the sensory epithelium (the olfactory, the sustentacular and the basal cells) may be destroyed by a 1 per cent solution of zinc sulfate and that only the nonsensory cells are replaced.

MOORE, Omaha.

THE NEED OF REDETERMINING SCHICK NEGATIVENESS IN SCHOOL CHILDREN. A. B. SCHWARTZ and F. R. JANNEY, J. A. M. A. **110**:1743 (May 21) 1938.

Schwartz and Janney found that of 145 children in whom the Schick test was negative 22 per cent showed a positive test six or seven years later. Consequently, they recommend that every child entering school be submitted to the Schick test or given an injection of toxoid in order to eliminate diphtheria.

HEERSMA, Kalamazoo, Mich.

CONTINUOUS NASOPHARYNGEAL SUCTION IN THE TREATMENT OF THE BULBAR TYPE OF POLIOMYELITIS. O. W. ANDERSON, J. A. M. A. **110**:2149 (June 25) 1938.

Bulbar paralysis, particularly in poliomyelitis, calls for aspiration of the secretions in the nasopharynx. Anderson describes a technic in which a rubber catheter and postnasal continuous suction are used to prevent pulmonary aspiration of these secretions.

HEERSMA, Kalamazoo, Mich.

POLIOMYELITIS VIRUS IN HUMAN STOOLS. J. D. TRASK, A. J. VIGNEC and J. R. PAUL, J. A. M. A. **111**:6 (July 2) 1938.

The authors offer criteria for identifying the virus of poliomyelitis. They found that intraperitoneal injections of suspensions of nasal or fecal material would produce the disease in monkeys. In the 4 cases in which virus was obtained the disease was abortive, mild, nonparalytic, and in 1 case the stools gave positive cultures for at least twenty-four days. These findings throw light on the epidemiology of the disease.

HEERSMA, Kalamazoo, Mich.

MENINGOENCEPHALITIS IN MUMPS. H. FINKELSTEIN, J. A. M. A. **111**:17 (July 2) 1938.

In 16 of 40 patients with mumps the spinal fluid was abnormal. Four patients had severe symptoms of meningeal irritation, while the rest had moderate symptoms or showed no clinical evidence of pathologic change. This investigation revealed that meningoencephalitis is a frequent accompaniment of mumps.

HEERSMA, Kalamazoo, Mich.

EVIDENCE OF ACTIVE IMMUNITY TO EXPERIMENTAL POLIOMYELITIS OBTAINED BY THE INTRANASAL ROUTE IN MACACUS RHESUS. S. D. KRAMER, L. H. GROSSMAN and G. C. PARKER, J. Exper. Med. **67**:529 (April) 1938.

The authors present the procedures and results of experiments which they believe are significant from an epidemiologic and a theoretic point of view and which perhaps have practical bearing on immunization against poliomyelitis.

Their studies have led them to believe that most persons who come in contact with the virus of poliomyelitis acquire immunity, only the occasional susceptible person succumbing to the paralytic disease. Events are very different in the experimental animal. Monkeys are essentially uniformly susceptible to experimental infection. With nasal instillations of a preparation of posterior pituitary for surgical use and of a preparation of epinephrine and ephedrine (adrephine) the authors were able to protect about two thirds of their animals against experimental intranasal infection. These measures definitely altered the susceptibility of the rhesus monkey. Moreover, most of the resistant animals which had received combined treatment with the preparation of posterior pituitary, adrephine and virus presented active immunity, as indicated by the presence of a neutralizing substance in their serum and by their ability to resist intracerebral infection. The authors admit that they have no knowledge of the mechanism by means of which the substances named produce the apparent alteration in susceptibility, but since the outcome of continued exposure to virus in most of the animals treated with these substances is immunity, it is believed that this form of treatment offers a more hopeful approach toward control of the disease.

KNICKERBOCKER, Dallas, Texas.

EFFECT OF VARIOUS BLOOD MEDIUMS ON THE GROWTH CHARACTERISTICS OF H. PERTUSSIS. J. A. TOOMEY and W. S. TAKACS, J. Infect. Dis. **62**:297 (May-June) 1938.

Freshly isolated cultures of Haemophilus pertussis begin early to lose their virulence and show morphologic change when grown on horse blood Bordet agar but retain their ability to produce specific agglutinins even after eighty-five generations. When such cultures are grown on sheep and human blood Bordet agar, the virulence begins to diminish slightly at eighty-five generations, but the morphologic character and ability to produce agglutinins in rabbits remain unchanged at this generation.

TOOMEY, Cleveland.

EFFECT OF WASHING AND PHYSICAL AGENTS ON H. PERTUSSIS. J. A. TOOMEY and W. S. TAKACS, J. Infect. Dis. **62**:313 (May-June) 1938.

When a disease-producing growth of Haemophilus pertussis that was continuously maintained on blood agar was washed repeatedly with physiologic solution of sodium chloride the operation removed a toxic factor and rendered the organism atoxic or avirulent for guinea pigs.

Under the conditions of this experiment, washing of the growth slightly changed also its ability to produce agglutinins of high titer in rabbits.

Incubation of the culture for from two to three hours did not destroy its virulence or toxicity for guinea pigs, while inactivation at 56 C. for two hours did.

Phenol in a concentration of 0.5 per cent and solution of formaldehyde U. S. P. in a concentration of 0.5 per cent rendered the culture less toxic or virulent for guinea pigs.

The frozen and powdered toxic fraction was not toxic or virulent for guinea pigs.

TOOMEY, Cleveland.

POLIOMYELITIS IN MINNESOTA IN 1937. J. F. POHL, Minnesota Med. **21**:392 (June) 1938.

This review of poliomyelitis in Minnesota covers a period of thirty years. It shows that there has never been a year when this disease has not been present to some degree and indicates that there is a fairly sustained expected annual level of the appearance of the disease, with significant increases appearing at fairly regular intervals. The annual mortality rate in a ten year period is 17.9 per cent. A study of the statistics indicates that either the virulence of the causative agent is subsiding or man is acquiring tolerance for it. However, the author points out that because of the difficulty of diagnosing the disease caution must be used in interpreting the statistics.

ANDERSON, Minneapolis.

PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **53**:747 (May 13) 1938.

For the period from March 27 to April 23, 1938, the incidence of measles decreased 24,000 cases. The peak was reached earlier this year than usual. The current incidence of measles has been the highest on record. The incidence of smallpox—1,882 cases—is the highest recorded since 1931. The number of cases of diphtheria was the lowest on record, and the incidence of influenza, meningitis, poliomyelitis, typhoid fever and scarlet fever continued low. The average mortality from all causes was 11.8 per thousand. The current rate is the lowest since 1931.

SANFORD, Chicago.

PROPHYLACTIC VALUE OF A SINGLE DOSE OF PRECIPITATED PERTUSSIS VACCINE. W. T. HARRISON, J. P. FRANKLIN and J. A. BELL, Pub. Health Rep. **53**:793 (May 20) 1938.

A commercially prepared pertussis vaccine was precipitated with alum. A dose of 1 cc. was injected into 82 children. A group of 109 unvaccinated children

were used as controls. Both groups were observed for one year. The reactions following the injections were negligible. In the vaccinated group the incidence of pertussis was 12 per cent and in the unvaccinated group 19 per cent. The pertussis occurring in the vaccinated group was milder. The authors agree, however, that the differences were too small and the groups too limited for them to draw conclusions. They believe that the results, in view of the small amount of antigen injected, justify an attempt to obtain further clinical evidence on a large scale. Such a trial is now in progress.

SANFORD, Chicago.

TANNIC ACID PRECIPITATION OF SCARLET FEVER TOXIN. M. V. VELDEE, Pub. Health Rep. **53**:909 (June 3) 1938.

Veldee reports the preparation of a purified and tannic acid–precipitated scarlet fever parent toxin. Its potency within titratable limits is the same as that of the purified soluble toxin or the cured toxin from which it is made. Amounts of 750, 3,000 and 10,000 skin test doses given at 2 week intervals are tolerated very well by children of grammar school age. Pupil nurses or persons of a similar age may be given 500, 2,000, 6,000 and 10,000 skin test doses. Children may be given a fourth dose if desired, another dose the size of the third dose or a still larger one being given.

SANFORD, Chicago.

PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **53**:935 (June 10) 1938.

For the period of April 24 to May 21 the incidence of smallpox remained high. There were 11,000 cases in 1937, and the first twenty weeks of 1938 indicated that the incidence would be twice that. The greatest numbers of cases were found in the west and northwest. The incidence of measles showed a decline but was still twice that of the two preceding years. The incidence of typhoid fever was slightly above normal. The incidence of meningitis, scarlet fever, diphtheria, influenza and poliomyelitis were below the seasonal average. The average mortality from all causes was 11.2 per thousand. This was the lowest since 1933.

SANFORD, Chicago.

PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **53**:1337 (Aug. 5) 1938.

In the period from June 19 to July 16, 1938, the incidence of measles was still above that in the corresponding period of last year but had decreased 60 per cent from that in the last four week period. The number of cases of smallpox was about 37 per cent higher, as was the incidence of influenza as compared with the current incidence. The figures for diphtheria, meningitis, poliomyelitis, scarlet fever and typhoid are below the median. The mortality rate from all causes was 10.3 per thousand.

SANFORD, Chicago.

GANGRENOUS VARICELLA. V. DELAVERGNE, Méd. inf. **9**:129 (May) 1938.

A child of 18 months contracted chickenpox. A few days later many of the lesions on the lower part of the abdomen and on the thighs contained hemorrhagic fluid. Several of the lesions developed into boils; Staphylococcus aureus was cultured from the pus. After fifty-six days the lesions had healed completely. The case was one of local infection of the pox, probably by organisms from the vagina or intestines. This type of gangrenous chickenpox must be differentiated from the type that is observed with a general constitutional abnormality and a purpuric diathesis.

HIGGINS, Boston.

STATISTICAL AND CLINICAL OBSERVATIONS ON CHILDREN WITH DIPHTHERIA TREATED IN THE PEDIATRIC CLINIC AT PALERMO DURING THE YEARS 1929-1937. G. MELODIA, Méd. inf. **9**:257 (Sept.) 1938.

Nine hundred and eighty cases of diphtheria were observed in nine years, the largest number in any one year being 136 and the smallest 81. Two hundred and two patients died (25.3 per cent). Diphtheria occurred in all months of the year, the largest number of cases being in the fall and early winter. Diphtheria was most common in children under 3 years of age and more common in boys than in girls.

Seven hundred and one cases involved the larynx. A higher mortality rate occurred with immediate tracheotomy than with immediate intubation. The best results were observed when intubation was followed in three days by tracheotomy, if the child had difficulty in breathing following extubation. The most frequent complication of diphtheria was bronchopneumonia.

HIGGINS, Boston.

BACILLARY DYSENTERY. J. M. DA ROCHA, Arch. de pediat., Rio de Janeiro **10**: 383 (May) 1938.

The organisms usually encountered as causes of dysentery in Brazil are the Shiga, Flexner-Hiss, Schmitz and Sonne. The period of incubation is from three to six days. The symptoms are gastric colic, dysentery and dehydration. These lead to secondary infections, as pyelocystitis and bronchopneumonia. The diagnosis is made from the results of bacteriologic examination and agglutination tests. The treatment is supportive, with fluids and with a diet of human milk and bland foods. Specific serums may be utilized, as well as constipating drugs in the forms of calcium carbonate, tannic acid and belladonna.

SANFORD, Chicago.

BULBAR ENCEPHALITIS COMPLICATING DIPHTHERIA. P. SCHRANK, Deutsche Ztschr. f. Nervenh. **144**:281, 1937.

A patient aged 32 had had fever, vomiting and headache for four days. He had a stumbling gait and nystagmus but no other definite neurologic signs. A day later he began to regurgitate liquids through the nose and saw double. Seven days after the onset he died. A culture from the nose was reported to be strongly positive for diphtheria bacilli. The brain was not remarkable except for multiple purulent and hemorrhagic spots in the floor of the fourth ventricle. These tiny abscesses were made up of leukocytes and lymphocytes clustered about veins. The brain was fixed in formaldehyde, and thus the possibility of recognition of the infective organism by culture was removed; special stains, however, showed bacteria with characteristic polar bodies. No bacteria could be seen in the cranial nerves. Only a single similar case has been reported (Sterling).

PUTNAM, Boston. [ARCH. NEUROL. & PSYCHIAT.]

NATURE AND TREATMENT OF WHOOPING COUGH. W. KELLER, Med. Klin. **34**: 253 (Feb. 18) 1938.

The therapy of pertussis cannot be placed on a mathematical basis because of the variable course of the disease and because of constitutional and other factors which must be considered. The results of vaccine therapy are difficult to determine because the relation of antibody formation to immunity is apparently not definite. According to Keller's observations, antibody formation after artificial immunization is similar to but more rapid than that occurring during the disease itself. However, even when prophylactic inoculation has led to antibody formation, protection against the disease is not assured. Sauer, to whom information and experience are available in large measure, reports good prophylactic results from the use of his specially prepared vaccine.

Vaccine therapy has some curative value. Rapid increase in antibody formation has been found to occur concomitantly with decrease in cough. Possibly there is an optimal time for vaccination during pertussis.

Continued critical effort to determine the effects of vaccine therapy is preferable to fruitless skepticism.

SIEMSEN, Chicago.

DIAGNOSIS OF WHOOPING COUGH. D. GAJZAGO and O. GOTTCHE, Monatschr. f. Kinderh. **73**:228 (May) 1938.

Of infants who have contracted whooping cough before the age of 6 months, from 25 to 30 per cent show a positive complement deviation. The reaction rarely occurs before the seventh to tenth week of the disease. Of children from 6 to 12 months of age, 73 per cent, and of children from 1 to 2 years, 85 per cent, show a positive reaction. In the case of older children positive results may be found by the fifth week. The reaction stays positive for from one to one and a half years.

The complement deviation test cannot be used with children who have been given preventive inoculations from three to four months previously.

Mothers of children with whooping cough frequently give a positive reaction, and in doubtful cases such a positive reaction may determine the diagnosis.

GERSTLEY, Chicago.

Acute Infectious Diseases

FURTHER STUDIES OF THE EXPERIMENTAL GONOCOCCAL INFECTION IN MICE AND THEIR PROTECTION BY SULFANILAMIDE. A. COHN and L. R. PEIZER, J. Infect. Dis. **63**:77 (July-Aug.) 1938.

The mouse may be used in studying chemotherapeutic effects on the gonococcus. So far only one route has been discovered by which the mouse may be infected, namely, the peritoneal. The important factors in experimental gonococcic infection in mice are the preparation of the mucin emulsion, the addition of the dextrose and the choice of the strain of gonococci. The mice used should weigh about 18 to 20 Gm.

The spread of gonococcic infection in the mouse follows multiplication of the organisms in the peritoneum, from which the gonococci invade the blood stream. After the removal of the peritoneal focus, the organisms disappear from the blood stream.

In current chemotherapeutic studies on gonococcus-infected mice it was found that feeding of sulfanilamide to mice protects them only if larger doses are fed than are necessary for subcutaneous injection. When a dose of 25 mg. of sulfanilamide was either fed or injected subcutaneously, an average of 65 per cent of the infected mice were protected.

TOOMEY, Cleveland.

BACILLARY DYSENTERY IN THE RHESUS MONKEY. W. S. PRESTON and P. F. CLARK, J. Infect. Dis. **63**:238 (Nov.-Dec.) 1938.

Spontaneous dysentery in laboratory monkeys is closely similar to dysentery in man. The etiologic agent that causes one common type of the human disease has been demonstrated in monkeys, with lesions and symptoms similar to those in man. Whether the disease occurs naturally in the monkeys or whether the organisms are acquired by contact with man cannot be stated without studying the animals in their native habitat. There is a possibility of healthy carriers among these animals. The isolation of Shigella paradysenteriae from 63 per cent of the animals of this series compares favorably with the figure given for the percentage of positive isolations from stools of human patients with the disease. This species of organism was the only type found with any regularity; the serologic findings and the artificial production of the disease add further evidence.

The Salmonella-like forms encountered were not studied in great detail. They constitute a rather heterogenous group and according to the authors, they should be investigated further to determine possible relationships with other Salmonella types. The motile, nongas-producing types seemed more closely related to the dysentery group and were given further attention, although they apparently had no causal relation to the monkeys' dysentery. These organisms have not been previously described.

The authors suggest that rhesus monkeys can be employed in studying some of the remaining problems of human dysentery to better advantage than can the lower experimental animals.

TOOMEY, Cleveland.

PROPHYLACTIC USE OF SERUMS AND VACCINES IN ACUTE BACILLARY DYSENTERY. J. FELSEN and A. G. OSOFSKY, J. Infect. Dis. **63**:298 (Nov.-Dec.) 1938.

From their observations the authors, taking into account the limited number of experimental animals used, draw the following inferences: Immune rabbit serums protected mice against 10 lethal doses of a moderately virulent strain of Bacterium dysenteriae. This protection was evinced when the protective serums were injected previously to, or at the time of, the inoculation of the organism. When the injection of serum followed the administration of the fatal dose of bacteria, no protection could be observed. Active immunization with vaccine also offered a considerable degree of protection.

TOOMEY, Cleveland.

TRICHINOSIS IN CLEVELAND: POSTMORTEM EXAMINATION OF DIAPHRAGM AND SKELETAL MUSCLE FROM ONE HUNDRED CONSECUTIVE AUTOPSIES. C. H. EVANS JR., J. Infect. Dis. **63**:337 (Nov.-Dec.) 1938.

The incidence of trichinosis in the Cleveland area is 36 per cent—as indicated by the results of examinations of diaphragms and skeletal muscles obtained at 100 consecutive autopsies.

The usual procedure of examining the diaphragms by the digestion–Baermann method alone revealed an incidence of 20 per cent. Application of the compression-microscopic and the digestion–Baermann methods showed variations in the number of organisms recovered but together gave a more nearly true result than either alone. Examination of skeletal muscles, such as the intercostal muscles and the sternocleido-mastoid muscle, in addition to the diaphragm gave a higher incidence of infestation than examination of the diaphragm alone.

TOOMEY, Cleveland.

FOCAL INFECTION AND METABOLISM: THE EFFECT OF THE REMOVAL OF TONSILS AND ADENOIDS ON THE NITROGEN BALANCE AND THE BASAL METABOLISM. J. A. JOHNSTON and J. W. MARONEY, J. Pediat. **12**:563 (May) 1938.

Nine children varying in age from 5 to 13 years were selected for study from among those currently admitted for tonsillectomy. All the children gave histories of recurrent infection of the throat and clinically showed evidence of previous infection of the tonsils. In none was there evidence of recent infection. The diets used were calculated from the food standards of Atwater and Bryant and Waller and were weighed in the diet kitchen of the hospital. The caloric intakes were designed, on the basis of previous studies, to maintain a positive nitrogen balance and a level or rising weight curve and were apportioned as follows: 15 per cent to protein, 35 per cent to fat and 50 per cent to carbohydrate. Determinations were made of urinary nitrogen daily and fecal nitrogen every three days by the Kjeldahl-Gunning procedure. The determinations of the basal metabolism were planned to correlate with each three day nitrogen balance; gas collections were made with the Tissot tank and analyses with the Haldane-Henderson apparatus. Tonsillectomy was performed with the subject under anesthesia induced with nitrous oxide and ether. In all except a single case a striking improvement in utilization of nitrogen followed the removal of the focus

of infection. The figures for the basal metabolism showed a definite fall following the operation; the lowest figures were obtained immediately following the operation, but the level of the basal readings, though higher after activity was resumed, continued lower than before the operation. The improvement in the utilization of nitrogen seems to be out of proportion to what might be accounted for as a result of a fall in basal metabolism incidental to the removal of the infection.

RAUH, Cincinnati.

A MALIGNANT PUSTULE IN A GIRL OF THREE. P. A. MORALIS, Arch. de méd. d. enf. **41**:573 (Sept.) 1938.

The author has had occasion to publish reports on numerous cases of anthrax among workers in the tanneries of the Balkan States during the past twelve years. Rarely, however, has a case in a child been reported. The observation herein discussed concerned a girl of 3 years.

Early treatment with specific serum in large doses, injected intramuscularly (daily during the acute stage), was followed by prompt recovery.

AMESSE, Denver.

RHEUMATIC DISEASE OF CHILDHOOD. J. SIEGL, Wien. klin. Wchnschr. **51**:429 (April 15) 1938.

Siegl reviews the causes, frequency and pathologic aspects of rheumatic disease and discusses diagnosis, differential diagnosis and treatment. In regard to the latter he notes that in the time-honored use of salicylates the tendency has been to underdose rather than overdose. He states further that the effectiveness of the salicylates in the treatment of rheumatic infections has been in the main disappointing and has led to a further search for a therapia sterilisans magna. He quotes the work of Helmreich, who supplemented salicylate therapy with a three month course of intravenous injection of a gold preparation. Occasional side reactions, such as fever and morbilliform eruptions, were noted, though gold preparations, he states, are only slightly toxic. The gold preparation mentioned is lopion, a proprietary product, the formula for which is not given in the article. [Lopion is sodium auroallylthiourea benzoate.—Ed.]

ABT, Chicago.

DYSENTERY BACILLEMIA. A. V. SCOTT, Chinese M. J. **53**:193 (Feb.) 1938.

Scott has found in the literature mention of 17 cases of sepsis from dysentery bacilli. She reports a case: An infant of 8 months had loose stools and a steadily diminishing weight. Petechiae began to appear on the legs. Death followed. Autopsy showed multiple ulcers of the intestinal mucosa, and a blood specimen gave a typical positive agglutination of streptococci.

NEFF, Kansas City, Mo.

RECURRENCE OF MONOARTICULAR TYPHOID OSTEOARTHROPATHY MANY YEARS AFTER THE ORIGINAL INFECTION. A. CANELLI, Acta pædiat. **20**:337, 1938.

A 6 year old child was prostrated by an illness characterized by fever and generalized arthralgia. Shortly after the onset clinical and roentgen examination revealed osteoarthropathy of the left hip. At the end of a month, typhoid fever was diagnosed from the blood cultures and serum agglutinations. The patient recovered without constitutional or local residuals. Ten years afterward, the original episode was duplicated in most of its details. Some disability of the hip persisted after the second attack. The author comments on the extremely rare character of this phenomenon.

MCCUNE, New York.

Chronic Infectious Diseases

CLINICAL USE OF QUANTITATIVE BLOOD TESTS FOR SYPHILIS. W. F. LORENZ, Wisconsin M. J. **37**:281 (April) 1938.

Lorenz, at the Wisconsin Psychiatric Institute, has adapted Eagle's microflocculation test to a quantitative procedure which he believes shows a great improvement over former methods. It aids not only in making the diagnosis but in determining the type of medication to be used, the progress made and to some extent the prognosis. With the newborn it is useful in differentiating between those who have syphilitic disease and those whose blood gives a positive reaction but who are without syphilitic infection. The latter condition is due merely to the passage of the reacting substance from the syphilitic mother to the infant. This may give a positive reaction during the first two months of the infant's life. On the other hand, a mother may have a negative reaction of the blood and still bear a syphilitic infant. In the case of the syphilitic pregnant woman a series of these quantitative tests should be made. Changes in the titer suggest the progress in treatment and the chances of having an infant free from syphilis. With adequately treated syphilitic women who are pregnant one can expect about 93 per cent of the offspring to be free from the disease. A quantitative test should be made on the blood of every newborn infant if the mother is, or has been, syphilitic.

Infants whose blood at birth gives a positive reaction but who present no clinical evidences of syphilis should not be treated immediately, but their blood should be tested every three days for the first three weeks. A falling titer means that the child is nonsyphilitic and a stationary or increasing titer, that there is infection. In a syphilitic newborn infant there may be a delay in the positive response; so, when there is reason to be suspicious, retesting at intervals is wise. The technical details of this quantitative method are given.

JANNEY, Wauwatosa, Wis.

SYPHILIS AND PREGNANCY. M. TRAUTMANN, Wisconsin M. J. **37**:286 (April) 1938.

Since it is estimated that from 10 to 20 per cent of all males in the United States (1919) are syphilitic, the lesser percentage of syphilis in unmarried females rapidly approaches that of syphilis in males soon after marriage. This makes congenital syphilis the largest single cause (Jeans) of death of fetuses at or before term. In a syphilitic family 75 per cent of the living children and 5 per cent of all infants are syphilitic.

The work of various authors is cited in estimating the prevalence of congenital syphilis in treated and in untreated mothers. In all such investigations there is shown a startling prevalence of syphilis, and the favorable influence on the infants of active treatment of pregnant mothers is just as striking. Among 1,000 consecutive stillbirths in Wisconsin, 334 were assigned to causes that might well have a relation to syphilis, i. e., 298 to unknown causes, 82 to maceration, 47 to hydrocephalus and so on. Since only 4 of the 1,000 were reported as syphilitic, it seems highly probable in the face of the known frequency that the Wassermann test is not being made often enough and that clinical observation with syphilis in mind is not being done well enough.

JANNEY, Wauwatosa, Wis.

PREVENTIVE MEDICINE AND CONTROL AND TREATMENT OF TUBERCULOSIS AS SEEN IN SOVIET RUSSIA. W. T. MUNRO, Edinburgh M. J. **45**:70 (April) 1938.

Munro writes of what he observed in a visit to Soviet Russia, where the structure of medical practice is socialized. Among his observations, he mentions child welfare stations and a crèche in Moscow and a preventorium in Karkov. Children seem to be carefully observed from the time of birth to the end of childhood. Parents leave their children at the institution while they are at work.

At the Children's Sanatorium in Kiev only children with pulmonary infections are accepted. They are from 8 to 15 years of age. Several of them had induced bilateral pneumothorax.

The bacteriologist at the Central Tuberculosis Institute in Moscow has been preparing a method of giving BCG by mouth. The attempt is made to give BCG to every newborn child.

NEFF, Kansas City, Mo.

PROGNOSTIC VALUE OF ZAMBRINI'S PTYALOREACTION IN TUBERCULOSIS. L. RICCITELLI, N. NICITA and A. CURZI, Gaz. d. hôp. **111**:381 (March 23) 1938.

The authors studied the value of Zambrini's salivary test in tuberculosis on 120 hospitalized patients. Simultaneous physical and roentgen examinations were made, and the whole course of illness was found correlated with the results of the test.

Although the theoretic foundation of the test is disputed, these workers regard the test as of great practical clinical value. Without giving numerical data, they state that the lower the values obtained with this test the less was the resistance of the patient to tuberculosis.

When the tuberculosis progressed, the salivary test always indicated this, and on several occasions it indicated a complication (pleurisy, hemoptysis) or an aggravation of the condition one or two days before the usual clinical symptoms (such as fever) revealed them.

The test is performed by collecting about 1 cc. of saliva in a clean, neutral, dry test tube (after the patient has rinsed the mouth from three to four times with distilled water) and adding to it from 15 to 20 drops of reagent. The color obtained varies from pale yellow to deep violet; high resistance to tuberculosis is indicated by the violet color.

KAJDI, Baltimore.

ANTITUBERCULOSIS CAMPAIGNS. T. AVERSA, Méd. inf. **9**:97 (April) 1938.

This article deals with the nature of childhood tuberculosis and with the methods of diagnosis and prophylaxis of this disease.

HIGGINS, Boston.

ROENTGEN STUDIES OF THE PRIMARY COMPLEX OF TUBERCULOSIS. M. FRANCISCO, Arch. de med. inf. **6**:365 (Oct.) 1937.

Francisco made a comparative study of the different theories regarding the primary infection and its development. He concluded that although the theories differ in terminology, in conception they are alike. On anatomopathologic considerations the concepts of Parrot and Ranke are most acceptable.

The importance of roentgenograms is stressed. Several should be taken.

SCHLUTZ, Chicago.

IMPORTANCE OF ROENTGENOLOGIC EXAMINATION OF INFANTS WITH SYPHILIS. C. LOPES DOMINGUES, Arch. de pediat., Rio de Janeiro **10**:337 (April) 1938.

Roentgenograms illustrative of syphilitic osteochondritis are shown.

SANFORD, Chicago.

TUBERCULOTOXIC MENINGITIS. E. KNOPF, Monatschr. f. Kinderh. **73**:82 (April) 1938.

The spinal fluid of 2 children with tuberculosis who showed mild meningeal symptoms showed a faintly positive reaction for protein and an increase in cell content. In a short time the symptoms disappeared. Knopf suggests that these were tuberculotoxic reactions.

GERSTLEY, Chicago.

Diseases of Blood, Heart and Blood Vessels and Spleen

AN ATTEMPT TO OBLITERATE THE PATENT DUCTUS ARTERIOSUS IN A PATIENT WITH SUBACUTE BACTERIAL ENDARTERITIS. A. GRAYBIEL, J. W. STREIDER and N. H. BOYER, Am. Heart J. **15**:621 (May) 1938.

A woman 22 years of age had an infection with Streptococcus viridans complicating patency of the ductus arteriosus. An attempt was made to obliterate the patent ductus in the hope of relieving the bacterial endarteritis. At operation the ductus was found to be so intimately attached by fibrous tissue to the pulmonary artery that it could not be freed, and an effort was made to close it with a series of plicating sutures. This resulted in reduction of the lumen, but obliteration was not complete. Four days after the operation the patient succumbed suddenly from acute dilatation of the stomach.

Autopsy revealed vegetations at the pulmonary orifice of the ductus and in the wall of the pulmonary artery.

The authors believe that in selected cases removal or obliteration of the patent ductus should be attempted before the appearance of heart failure or of subacute bacterial infection.

GIBSON, Chicago.

HEART SOUNDS IN NORMAL CHILDREN. M. H. MCKEE, Am. Heart J. **16**:79 (July) 1938.

In order to establish normal standards, stethographic records were made on 105 apparently healthy school children. Four distinct sounds invariably accompanied each heart beat, namely, the first, the second, the "physiologic" third and a supposedly auricular sound, which preceded the first. The last-named two were low in pitch and usually of little intensity, and therefore were generally inaudible. The first or the second sounds or both were frequently split.

Sinus arrhythmia was always present. The differences in the intersphygmic intervals depend on the time elapsing between the third sound and the following auricular sound. The intensities of the various sounds depend on where the microphone is placed and vary greatly with changes in the cardiac rate.

At the apex, a moderately low-pitched, usually faint systolic murmur was present in all instances, which suggests that too much significance should not be attached to such murmurs when they are barely audible with the stethoscope. No diastolic murmurs were encountered.

This investigation indicates that splitting of the first or second heart sound and the presence of a third sound have no pathologic significance.

FROM THE AUTHOR'S SUMMARY [GIBSON, Chicago].

HEART SOUNDS AND MURMURS IN CHILDREN WITH RHEUMATIC HEART DISEASE. M. H. MCKEE, Am. Heart J. **16**:88 (July) 1938.

Stethograms of 119 children with organic heart disease showed abnormally loud second sounds at the pulmonic area in 19 per cent. Otherwise the heart sounds were not outside the normal range.

Apical systolic murmurs which were present in cases of mild cardiac damage appeared similar to those found in normal records except for increased intensity. With more advanced heart disease these murmurs became slightly higher pitched.

Apical diastolic murmurs in children whose heart disease is not far advanced may come and go from time to time during periods of apparent inactivity of the disease or even during varying phases of respiration.

GIBSON, Chicago.

FURTHER OBSERVATIONS ON APICAL SYSTOLIC MURMURS IN CHILDREN. L. G. STEUER and M. H. FINEBERG, Am. Heart J. **16**:351 (Sept.) 1938.

Of 33 children with apical systolic murmurs who were followed for more than ten years, 27 per cent acquired serious valvular heart disease (chiefly mitral

stenosis), 61 per cent still had systolic murmurs and nothing more, and 12 per cent lost their murmurs entirely.

Those who acquired mitral stenosis did so between 1 and 9 years of age (usually between 4 and 6 years) after the discovery of the original murmur.

A slight elevation of temperature in a child with an apical systolic murmur is of no significance as a prognostic sign. It is possible that in children with apical systolic murmurs there is an abnormal tendency for early hypertension to develop.

Conclusions drawn after following 100 children with systolic murmurs for six years were unshaken by following 33 of the same children for an additional period of four years or more. AUTHOR'S SUMMARY [GIBSON, Chicago].

IS COBALT OF ANY SIGNIFICANCE IN THE TREATMENT OF MILK ANEMIA WITH IRON AND COPPER? E. J. UNDERWOOD and C. A. ELVEHJEM, J. Biol. Chem. **124**:419 (July) 1938.

In rats with anemia induced by a diet exclusively of milk Underwood and Elvehjem investigated the hemoglobin response to cobalt-free iron and copper, to unpurified iron and to additional amounts of cobalt. They found no difference in the hemoglobin response in the three groups of rats. They believe the traces of cobalt found in milk are probably sufficient to take care of the animal's needs.

LIMPER, Louisville, Ky.

RELATIONSHIP OF RHEUMATIC FEVER TO SUB-ACUTE BACTERIAL ENDOCARDITIS. J. A. HOLMES, New Orleans M. & S. J. **90**:71 (June) 1938.

Holmes gives a good brief review of the literature on the causes of both rheumatic and subacute bacterial endocarditis. It is shown that the bacteriologic causes of rheumatic endocarditis are unknown. In subacute bacterial endocarditis the etiologic agent is Streptococcus viridans in 95 per cent of the cases.

Although apparently due to different organisms, subacute bacterial endocarditis is shown to be usually (in from 65 to 90 per cent of cases) secondary to previous rheumatic endocarditis. It is pointed out that on the basis of experimental, bacteriologic, immunologic and pathologic evidence these diseases seem to be related.

BERKLEY, Los Angeles.

TREATMENT FOR SPLENIC ANEMIA AND BANTI'S SYNDROME. L. HOWELLS, Lancet **1**:1320 (June 11) 1938.

All patients admitted to the London Hospital from 1907 to 1935 with the diagnosis of splenic anemia or Banti's syndrome were subjected to detailed scrutiny. Of the 129 whose symptoms and signs were surveyed, 35 failed to fulfil the requirements. Of the remaining 94 patients, 51 were treated by splenectomy. It was concluded that splenectomy did not improve the expectation of life and did not prevent the progress of the cirrhosis or of the anemia or the occurrence of hematemesis.

LANGMANN, New York.

CONGENITAL ISOLATED DEXTROCARDIA DEVELOPING AURICULAR FLUTTER. H. DAVIS, Lancet **1**:1331 (June 11) 1938.

Congenital dextrocardia without transposition of the other viscera is reported in a 41 year old woman. Auricular flutter developed, with congestive heart failure and terminal septicemia. The observations at necropsy suggested that the dextrocardia was due to a rotation of the long axis of the heart in a clockwise direction so that the left ventricle lay anteriorly. There was an abnormal relationship of the pulmonary artery and the aorta.

LANGMANN, New York.

DIAGNOSTIC SIGNIFICANCE OF ORTHODIAGRAPHY. M. DE BIEHLER, Arch. de méd. d. enf. **41**:495 (Aug.) 1938.

Orthodiagraphy was introduced as a complement to roentgenoscopy by Moritz, in 1900, and carried forward through the investigations of Bardet, Duhem and others.

In urging this method of examination in cases in which cardiac disease, congenital or acquired, is suspected, the author reports observations in cases of organic disorders and offers several case histories to demonstrate the value of the procedure.

AMESSE, Denver.

A RARE CASE OF CARDIAC ARRHYTHMIA IN A GIRL OF SEVEN YEARS. V. MIGLIORI, Riv. di clin. pediat. **36**:694 (Aug.) 1938.

The patient had previously had hemichorea and rheumatic heart disease with mitral insufficiency. A recurrence of the arthritis occurred during an attack of scarlet fever. The child then showed a gallop rhythm, with a pulse rate of between 120 and 160 per minute. Later there was a sudden and surprising change to bradycardia and a pulse rate of 70. This arrhythmia later disappeared and was defined as bathmotropic by Migliori.

The electrocardiograms are reproduced and demonstrate regularly recurring auricular premature beats following the QRS waves; these beats were usually blocked because of their early prematurity and because of the fact that the ventricle was still refractory. The tracings are unusual and therefore of considerable academic interest.

HIGGINS, Boston.

LEDERER'S ANEMIA. A. CARRAU and M. E. MANTERO, Arch. de pediat. d. Uruguay **9**:227 (April) 1938.

A case of acute anemia in a 7 year old boy is reported. Improvement occurred after two blood transfusions and intramuscular injections of liver. The diagnosis of Lederer's anemia was made. However, an intercurrent varicella developed and led to the death of the child on the fortieth day after his admission to the hospital.

SCHLUTZ, Chicago.

TRANSPOSITION OF THE GREAT VESSELS. G. CARDELLE, F. BORGES and B. SANCHEZ SANTIAGO, Bol. Soc. cubana de pediat. **10**:195 (May) 1938.

The importance of the angiocardiographic procedure (in which a radiopaque material is injected intravenously) is emphasized. The authors were able to diagnose congenital malformation of the heart in a 13 day old infant. The anomaly consisted of patency of the interventricular septum and transposition of the aorta.

SCHLUTZ, Chicago.

ROGER'S DISEASE IN INFANTS. G. CARDELLE, B. SANTIAGO and R. P. REYES, Bol. Soc. cubana de pediat. **10**:259 (May) 1938.

The authors present a case in which Roger's disease was diagnosed by the angiocardiographic technic, the finding being a patent interventricular septum, which was revealed by both direct and indirect signs. The disease is not rare. In the majority of the cases it is compatible with life.

SCHLUTZ, Chicago.

INTERAURICULAR COMMUNICATION DIAGNOSED BY AN ANGIOCARDIOGRAPHIC TECHNIC. A. CASTELLANOS, R. PEREIRAS and A. GARCIA, Bol. Soc. cubana de pediat. **10**:277 (May) 1938.

A detailed description is given of the angiocardiographic technic (radiopaque material injected intravenously) for determination of the anatomic condition of the

cavities of the right side of the heart post mortem. A typical case is cited in which the condition was thus diagnosed and then confirmed by autopsy.

SCHLUTZ, Chicago.

DIAGNOSIS OF CONGENITAL HEART DISEASES. R. REYES and H. TORRE, Bol. Soc. cubana de pediat. **10**:293-304 (May) 1938.

In the Infant's Hospital, Habana, Cuba, use is being made of a valuable diagnostic aid for the detection of congenital cardiac diseases, namely, angiocardiography with radiopaque materials. The accuracy and rapidity of the results are emphasized. The procedure was first described by Castellanos and Pereiras.

SCHLUTZ, Chicago.

MORBUS MACULOSUS WERLHOFII (PURPURA HAEMORRHAGICA); VITAMIN A DEFICIENCY AND THROMBOCYTOSIS. E. SCHIFF and C. HIRSCHBERGER, Jahrb. f. Kinderh. **147**:81 (July) 1936.

Observations on both man and rats enable the authors to state that vitamin A has no influence on the production of thrombocytes. A fat-soluble "T" factor contained in sesame oil is the activator in preparations of vitamin A.

LANDAU, Hannibal, Mo.

CONGENITAL HEART DISEASE: ROENTGENOLOGIC AND CLINICAL DIAGNOSTIC AIDS. I. HECKO and O. VYCHYTIL, Časop. lék. česk. **75**:921 (July 17) 1936.

The authors present 22 cases of congenital heart disease, in 20 of which clinical observations were checked by autopsy, and in addition they present 2 cases of idiopathic cardiac hypertrophy. The diagnoses were: transposition of the great vessels (8 cases), isolated septal defect of the auricle (4 cases), stenosis of the aortic isthmus (4 cases, in 1 of which there was an associated interventricular septal defect), combined interventricular and interauricular defects (2 cases), combined patent ductus Botalli and interventricular septal defect (1 case), stenosis of the pulmonary artery (1 case) and a fibrous anomaly of the tricuspid valve (1 case). The antemortem diagnosis was correct in 5 cases. The roentgenograms are of less value in diagnosing congenital heart disease in the newborn than in older infants. The value of cyanosis and the qualities of the murmurs are discussed. It is possible that in some cases the murmur is intensified by a superimposed functional murmur.

STULIK, Chicago.

Diseases of Nose, Throat and Ear

DEAF-MUTISM: CONSIDERATION OF ITS CAUSES AND GENESIS. R. LABBÉ, Arch. de méd. d. enf. **41**:257 (May) 1938.

The study of deaf-mutism is of the deepest interest whether one approaches it from a medical, an educational or a social point of view. There were 18,801 deaf-mutes in France in 1926, giving a ratio of 47 to each 100,000 inhabitants. In 1851 the proportion of deaf-mutes was 82 to each 100,000. These statistics are in striking contrast with those relating to blind persons, whose numbers have been steadily increasing during the past thirty years.

Labbé, as chief of the National Institute of Paris, reports his observations on 150 of the 263 pupils, whose ages range from 7 to 20 years. These subjects have been received not only from every portion of France but from foreign countries and represent all social groups. The dictum of Aristotle is reaffirmed: Deafness is the primary defect and mutism a sequel. Among the questions which naturally arise in the study of these children are: What is the degree of deafness? Is it congenital? What is its origin?

Castex and Thallon have suggested the following classification: (1) congenital deaf-mutism; (2) acquired deaf-mutism; (3) deafness occurring late without mutism, and (4) mutism without deafness. The proportions of these various categories at the Paris training school were, respectively, 47.9, 46.9, 4.16 and 0.8 per cent.

The etiologic facts of deaf-mutism are obscure; in spite of the view commonly held concerning the influence of syphilis, this is not in evidence in the great majority of cases. In cases of congenital deaf-mutism, one is prone to assume that maternal trauma may be a factor, although endocrine disturbance seems more rational. Patients suffering from acquired deaf-mutism, while occasionally showing results of injury, more frequently trace their disability to rhinopharyngeal or otitic infections in early infancy. It is obvious that the difficulties of reconstituting the history of such deaf-mutism are numerous and often insurmountable. Comby declared that acute encephalitis in this period of life spares the auditory apparatus more frequently than one has been led to believe; all authorities, however, stress the baneful influence of cerebrospinal meningitis in this regard. Here the deafness is practically always bilateral and complete. In this connection it is interesting to note that the percentage of deaf-mutism in Switzerland is six times as great as that in Belgium, which brings up the question of climate and of frequent colds.

Labbé discusses at length the importance of family predisposition to deafness and also seeks to clarify conceptions of heredity as a causative agent. Malformations of the inner and middle ear are likewise given proper consideration.

AMESSE, Denver.

THE PNEUMOPHONE, AN APPARATUS FOR MEASURING THE PRESSURE IN THE MIDDLE EAR. H. A. E. VAN DISHOECK, Nederl. tijdschr. v. geneesk. **82**:13 (Jan. 1) 1938.

When a sound of constant intensity is conducted by way of the air or the bone to the ear, it is possible, if the air pressure in the external auditory meatus is gradually lowered from positive to negative, to mark off a special zone of most distinct hearing (Z. D. H.). On this principle a small apparatus, the pneumophone, was built for clinical purposes. It appeared that the Z. D. H. in normal ears extends from $+2$ to -2 cm. of water pressure. In the case of catarrh of the eustachian tube after a tonsillectomy or a nasal operation, the Z. D. H. was found to be negative, for instance, from -16 to -20 cm. of water pressure. Directly after air insufflation and before swallowing, a strongly positive Z. D. H. was found, for instance $+10$ to $+14$. Therefore the Z. D. H. is a means for the quantitative diagnosis of tubal stenosis and a check on the effect of insufflation. In the case of perforation of the ear drum and in the case of ankylosis of the stapes there is no Z. D. H. at all. For the diagnosis of ankylosis of the stapes the test with the pneumophone must be preferred to the unreliable results of the test of Gellé.

VAN CREVELD, Amsterdam, Netherlands.

A "NOSE-PLETHYSMOMETER" FOR USE IN DIAGNOSING OBSTRUCTION OF THE SIGMOID SINUS AND OF THE JUGULAR VEIN. H. A. E. VAN DISHOECK, Nederl. tijdschr. v. geneesk. **82**:277 (Jan. 15) 1938.

On obstruction of one jugular vein by unilateral compression of the neck, one observes a swelling of the inferior concha of the nose on the same side. This symptom has its origin in congestion of the pterygoid plexus by the venous blood coming from the endocranium. In a few cases this symptom can be found by anterior rhinoscopic examination. By means of a specially constructed "nose-plethysmometer," the swelling of the nose can be detected in nearly every case. As a consequence, this phenomenon can be used as a symptom of obstruction of the jugular vein and of the sigmoid sinus in cases of thrombosis, of pressure by

tumor or abscess of the brain and of congenital absence of the sinus or of the jugular vein. In the latter case, on the side of the obliteration the symptom will be negative while on the other side it will be strongly positive.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Lungs, Pleura and Mediastinum

SPUTUM TYPING IN PNEUMONIA IN INFANTS. N. HIRSCHBERG, Arch. Pediat. **55**:521 (Sept.) 1938.

Pneumonia in infants may be due to various organisms. Stomach washings from 23 infants under 1 year of age were typed by the Neufeld method. At the same time cultures were made from the same specimens, to be examined six hours later by the Neufeld reaction. When no positive typing occurred by either of these methods, the cultures were incubated for a longer period to ascertain the presence of pneumococci too few to be typed by the direct method or to determine the presence of other bacteria.

Only 2 of the 23 specimens showed pneumococci. From the other 21 specimens all types of bacteria that are usually found in the adult nose and throat or in the lungs were isolated.

In 9 of 15 infants who came to autopsy pneumococci were shown to be the predominating organisms.

In a second series 65 laryngeal swabs were taken in the same manner. Pneumococci were demonstrated in 19 instances; in 17 the organisms were typed by the direct method; in 2, after routine culture.

The apparent lack of success might be due to absence of pneumococci, rather than to inefficient methods.

Forty-four cases of pneumonia in adults, in which various types of pneumococci had been typed directly from the sputum, were studied. The throat of each patient was swabbed before a coughing spell had freshly contaminated the throat. Pneumococci of the type found in the sputum were isolated from 15, or 34 per cent, of these persons. In no instance was a different type of pneumococci recovered.

Nineteen persons with pneumococci in the pleural fluid were studied. Only 2 were shown to have the organisms in the throat. One of 12 patients with pneumococcic meningitis was shown to have the organisms in the throat. Throat swabs from 2 of 10 patients with pneumococcic septicemia showed the organisms.

Routine cultures will eliminate the relatively expensive and time-consuming procedure of typing material obtained from throat swabs in which no pneumococci are present.

ORR, Buffalo.

LUNG ABSCESS AND ITS RELATION TO SURGERY OF THE UPPER RESPIRATORY TRACT. H. MORRISON, New England J. Med. **218**:669 (April 21) 1938.

The otolaryngologist rarely, if ever, sees pulmonary abscess as a complication in his operative cases. Studies of large series of cases of tonsillectomy show pulmonary abscess occurring on the average once in 2,000 or 3,000 cases.

In 1925 Lord reported 227 pulmonary abscesses observed at the Massachusetts General Hospital between 1909 and 1924. Of these, 96 (42 per cent) followed operative procedures; 78 (34 per cent) followed operations on the upper respiratory tract, of which 21 (9 per cent) occurred after the extraction of teeth, 49 (22 per cent) after tonsillectomy, and the remaining 8 after operations elsewhere. Aspiration of foreign bodies was responsible for 8 abscesses. In this series 28 (12 per cent) of the abscesses were ascribed to pneumonia. One followed esophagoscopic examination. The cause of the rest was not determined.

From the point of view of the prevention of abscess of the lung, several propositions stand out: Tonsillectomy and other operations on the nose and throat are major surgical procedures. They should be performed in a hospital, and the

patients should be carefully followed. Local anesthesia is preferable to general, but more important than the type of anesthesia is the qualification of the anesthetist. It is well established that the danger of pulmonary abscess after tonsillectomy is much greater in adults than it is in children.

Extractions of teeth should be done in several sessions, obviating general anesthesia and too large a wound, and also minimizing the danger of aspiration of a foreign body.

GENGENBACK, Denver.

TREATMENT OF ASTHMA IN CHILDHOOD. C. P. LAPAGE, Practitioner **141**:318 (Sept.) 1938.

Asthma is due to a combination of several causes. There may be local lesions in the lung following an attack of pneumonia in early life; spots of irritation may be present in the nose, throat or bronchial glands; sensitization to some special protein may have taken place. But there is also an underlying dispositional tendency to metabolic error with a consequent disturbance of the autonomic nervous system.

Palliative Treatment.—Lapage recommends administration of epinephrine inhalants and antispasmodics, change of climate and other measures.

Preventive Treatment.—Three measures are advised: (1) removal of immediately exciting factors by: (*a*) treatment of the local lesion, e. g., bronchiectasis, chronic bronchitis or a sensitive nasal membrane; (*b*) avoidance of special irritants, such as pollens, foodstuffs and house dust, or, alternatively, desensitization.

2. Removal of health-lowering foci of sepsis, such as infected tonsils, adenoids and teeth, and operative antral or sinusal sepsis, nasopharyngeal catarrh, bronchiectasis and chronic infection of the bowel.

3. Use of general measures, such as the production of shock by means of peptones and tuberculin, which may raise the serum resistance to external factors, and of general health measures such as the application of ultraviolet rays and visits to regions with suitable climates.

4. Attention to metabolism to prevent accumulation of fatty acids in the blood and attacks of hepatic origin.

5. Cultivation by exercises of body control and of habits of thought which lead to ordered control of the autonomic nervous system. Such control tends to eliminate the undesirable reflex, which asthma is, or to remodel it into something less disturbing.

The outlook for asthma in childhood is often good if treatment is based on the preventive lines of gradual reestablishment of metabolic tolerance and educational establishment of control of the autonomic nervous system.

GELSTON, San Francisco.

SUFFOCATIVE CATARRH. J. CATHALA, P. AUZÉPY and A. BRAULT, Rev. franç. de pédiat. **14**:105, 1938.

The authors describe two types of suffocative catarrhal infection. The first, which suggests a plugging of the bronchi, may result in sudden recovery or sudden death. The second type has a more uniformly bad prognosis, with a pathologic picture resembling capillary bronchitis or bronchopneumonia.

LESLIE, Evanston, Ill.

PNEUMONIA IN INFANTS. C. GIANELLI and E. PELUFFO, Arch. de pediat. d. Uruguay **9**:269 (May) 1938.

Gianelli and Peluffo present 2 cases of pneumonia in infants in which the disease was frank and definite but the temperature curves were irregular from the onset until recovery. This finding could not be attributed to the presence of any complications.

SCHLUTZ, Chicago.

ALLERGIC INFILTRATION OF THE LUNGS IN BRONCHIAL ASTHMA. W. BECKER, Kinderärztl. Praxis **9**:322 (Aug.) 1938.

In a 2 year old child suffering from a severe attack of bronchial asthma, a roentgenogram showed a rather dense infiltration of the right hilar region of the lung. The child had no fever. The reaction to tuberculin (1 : 10) was negative. There was no leukocytosis. The sedimentation rate was 11 mm. per hour. These findings speak against pneumonia and tuberculosis and in favor of an allergic phenomenon.

HEYMANN, Cleveland.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

A SIMPLE TEST FOR DETERMINING THE PRESENCE OF GASTRO-INTESTINAL LESIONS —A PRELIMINARY REPORT. E. E. WOLDMAN, Am. J. Digest. Dis. **5**:221 (June) 1938.

Phenolphthalein in a dose of 0.1 Gm. is given by mouth on an empty stomach, and specimens of urine are obtained at two and four hour intervals afterward. A six hour specimen may be necessary in cases of acute or chronic nephritis, cardiac failure, fever or dehydration.

One gram of white phenolphthalein is dissolved in 100 cc. of 95 per cent alcohol. The dose administered is 10 cc. of this 1 per cent solution, diluted to 30 cc. with water to make it more palatable. Ten per cent sodium hydroxide is added to the urine, which should be examined promptly to avoid false positive reactions.

This test was carried out on 112 subjects, 77 of whom had no apparent gastrointestinal lesions. Of the 35 patients with lesions, 34 had a positive test for phenolphthalein in the urine; the patient who did not have a positive test had roentgenographic evidence of an irregular duodenal cap and had pain one-half hour after meals which was relieved by food but not alkalis. This patient may not have had an active lesion. Of the 77 patients with no apparent gastrointestinal lesion, 75 exhibited no evidence of phenolphthalein in the urine after two and four hours. Two of these 77 patients were too ill to check thoroughly for the presence or absence of a gastrointestinal lesion—one had multiple sclerosis and the other coronary thrombosis. Permission for an autopsy on the patient who died was refused. The possible error in a series of 112 cases was approximately 2.7 per cent.

MORRISON, Savannah, Ga.

THE TAKATA REACTION IN THE BLOOD SERUM. E. WAYBURN and C. B. CHERRY, Am. J. Digest. Dis. **5**:231 (June) 1938.

This test is highly technical. A positive result indicates a dysfunction of the liver. It is a mercury bichloride flocculation test. In 94 cases of cirrhosis of the liver there were 87 positive reactions, a percentage of 92.5.

MORRISON, Savannah, Ga.

THE EARLY DIAGNOSIS OF NON-TROPICAL SPRUE, WITH A NOTE UPON ITS FAMILIAL INCIDENCE. G. L. WELLER JR., Am. J. Digest. Dis. **5**:254 (June) 1938.

This is a report of 4 cases of nontropical sprue. One instance was apparently accompanied by other cases of nontropical sprue in the family. Little has been written about the familial incidence of sprue.

Liver extract apparently is a specific for sprue.

The diagnosis of nontropical sprue is suggested by a history of increased frequency of bowel movements, abdominal distress and exacerbation of intestinal peristalsis after ingestion of certain foods. In addition, examination of the stool reveals only soft material or partially undigested foods but never blood or pus.

The final point in diagnosis is that of increased mobility of barium sulfate in the intestinal tract, so that it reaches the sigmoid at the end of from three to four hours after ingestion. Males and females seem to be affected in equal proportions.

MORRISON, Savannah, Ga.

"COLIC" OR FISSURE IN ANO. H. C. ARCHIBALD, Arch. Pediat. **55**:252 (April) 1938.

An anal fissure may be the source of pain in an infant. Four cases are presented.

ORR, Buffalo.

AN OUTBREAK OF JAUNDICE IN DETROIT. J. G. MOLNER and J. A. KASPER, J. A. M. A. **110**:2069 (June 18) 1938.

Seventeen cases of jaundice occurred among children and concurrently several among dogs in a Detroit epidemic. The findings in a fatal case in a 3 year old child are reported, including the identification of Spirochaeta icterohaemorrhagica. The serum of this child caused agglutination of the spirochetes.

HEYMANN, Cleveland.

A BACTERIOLOGIC STUDY OF LIVER ABSCESSES IN CATTLE. I. E. NEWSOM, J. Infect. Dis. **63**:232 (Nov.-Dec.) 1938.

Newsom reports that most abscesses seen in the livers of slaughtered cattle are due to an invasion of the livers by Actinomyces necrophorus. Occasionally Corynebacterium pyogenes and a white coccus may also be present.

TOOMEY, Cleveland.

NEW INTERMEDIATE BACTERIEAE FROM THE INTESTINAL TRACT OF THE RHESUS MONKEY. W. S. PRESTON and P. E. CLARK, J. Infect. Dis. **63**:234 (Nov.-Dec.) 1938.

Sixteen strains of previously undescribed motile rods, gram-negative and not fermenting lactose, have been isolated from the intestinal tracts of rhesus monkeys. They represent new species of the tribe Bactericae. They show closest cultural similarity to, but no antigenic relations with, the genus Eberthella.

TOOMEY, Cleveland.

BANANA AND BANANA POWDER THERAPY IN DIARRHEAL DISEASES OF INFANTS AND YOUNG CHILDREN. E. A. SOCOLA, New Orleans M. & S. J. **91**:192 (Oct.) 1938.

Following the lead of Joslin, Brubaker and European investigators, Socola reports his experience with (1) fully ripe bananas creamed, and (2) banana powder. The total number of cases in which studies were completed are classified as follows:

1. Dietetic diarrhea—31 cases.
   (*a*) Mechanical (simple diarrhea due to ingestion of some specific indigestible food)—5 cases. In this group the results were excellent. The condition cleared in 4 within twenty-four hours and in the fifth in forty-eight hours. All the children were over 1 year of age.

(*b*) Putrefactive (attributed to indigestion of protein)—5 cases. The results were excellent; all the children showed prompt clearing and gained in weight. All were over 1 year of age.

(*c*) Fermentative (due to indigestion of carbohydrate)—21 cases. Ten of the patients were over and 11 under 1 year of age. All gained weight. The results may be classified as follows: excellent in 18, fair in 2 and poor in 1.

2. Infectious diarrhea—15 cases. The results were excellent in 12 and fair in 3. Eleven children gained weight.

3. Parenteral diarrhea—30 cases. The results were excellent in 22, fair in 4 and poor in 4.

4. Bacillary dysentery—2 cases. The results were excellent in 1 and poor in 1.

Socola concludes that banana therapy is safe, practicable and efficient in the diarrheas of infants and young children.

BERKLEY, Los Angeles.

"PRIMARY" STREPTOCOCCIC PERITONITIS TREATED WITH SULFANILAMIDE. J. S. HORSLEY and D. G. CHAPMAN, South. M. J. **31**:999 (Sept.) 1938.

Horsley and Chapman present the case of a 13 year old boy who was critically ill from "primary" streptococcic peritonitis. He made a spectacular recovery following operative drainage and the administration of 100 cc. of a 2.5 per cent solution of prontosil (the disodium salt of 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonic acid) and 20.8 Gm. of sulfanilamide over a period of nine days.

SCHLUTZ, Chicago.

RADIOLOGY IN THE DIAGNOSIS OF HYPERTROPHIC PYLORIC STENOSIS. L. FINDLAY, Arch. Dis. Childhood **13**:145 (June) 1938.

The current opinion regarding the value of roentgenologic examination in the diagnosis of hypertrophic pyloric stenosis is discussed. The observations in 12 children with hypertrophic pyloric stenosis and in 12 normal children after a barium sulfate meal are described. While the motility of the stomach is shown to be as a rule impaired in hypertrophic pyloric stenosis, this is not the invariable rule. In some stomachs showing hypertrophic pyloric stenosis the motility is as good as in the normal stomach. When the time involved in this method of examination and the variability of the observations are considered, the only justifiable conclusion is that it has no place in the diagnosis of hypertrophic pyloric stenosis. The most reliable evidence of hypertrophic pyloric stenosis is the presence of a tumor. A palpable tumor is present in all cases.

KELLY, Milwaukee.

DUODENAL ATRESIA; GASTRO-ENTEROSTOMY; RECOVERY. K. H. TALLERMAN and D. LEVI, Proc. Roy. Soc. Med. **31**:761 (May) 1938.

Duodenal atresia and gastroenterostomy, followed by recovery, are reported in a child fourteen weeks after operation. The child was submitted to operation at the age of 6 days. At the time of the report the patient was doing as well as any normal child. The full details of the operation and notes on the patient's daily progress, including the treatment and feeding, are given.

WILLIAMSON, New Orleans.

PYLORIC STENOSIS IN AN INFANT AGED FIVE MONTHS. C. HARRIS, Proc. Roy. Soc. Med. **31**:767 (May) 1938.

Rammstedt's operation was performed on a 5 month old child. The infant made an uneventful recovery.

WILLIAMSON, New Orleans.

CERVICAL ADENOPATHY DISCLOSING A PHARYNGEAL EPITHELIOMA IN A BOY OF NINE YEARS. M. CONDAT, J. GADRAT and J. LASSERRE, Arch. de méd. d. enf. **41**:563 (Sept.) 1938.

Neoplastic adenopathies, frequent enough in adults, are extremely rare in children. The writers report a case of voluminous cervical adenopathy which for several months was the sole manifestation of latent epithelioma of the pharynx. Cervical adenitis followed an attack of measles; the origin was at first considered tuberculous, and the boy was subjected to radiotherapy, without visible improvement. When he entered the hospital a painless mass was noted occupying the entire lateral aspect of the right cervical region; the skin was not adherent. On the left side three small nodules presented along the course of the jugular vein, but no further ganglionic area was involved. Examination of the posterior pharyngeal wall revealed a tumefaction, particularly noticeable toward the right. Histologic investigation following removal of one of the small glands of the left cervical region and of tissue from the pharyngeal tumor showed identical evidence of a basocellular epithelioma, springing primarily from the mucosa of the pharynx.

The evolution of the neoplasm was rapid; the boy became dyspneic, and a fatal hemorrhage terminated life seven months after the cervical adenopathy was first noted.

AMESSE, Denver.

PAROTITIS STREPTOTRICHOMYCOTICA: REPORT OF A CASE. O. HNEVKOVSKY, Arch. de méd. d. enf. **41**:569 (Sept.) 1938.

Infection with Streptothrix is so rare that its presence in a given case is usually unsuspected. The second case of parotitis due to this organism is discussed in the contribution of Hnevkovsky. A previous instance was reported by Frotzel, in 1934. Streptothrix is a saprophyte primarily and is only exceptionally identified in acute processes of the respiratory or the gastrointestinal tract; in this respect streptotrichosis resembles actinomycosis. Both infections are likewise relieved by the iodides.

The case in question concerned a girl of 14. The first symptoms noted were difficulty in opening the mouth and a dull pain over the right parotid area. Examination of the blood revealed nothing, as also investigations into the possibility of tuberculosis and syphilis. After three weeks, radiation was applied, and this was repeated, small doses being employed. Following this, fluctuation was noted, and four small incisions were made. A yellowish white discharge from two of these incisions revealed the presence of Streptothrix in pure culture. Intensive treatment with potassium iodide resulted in prompt and permanent relief.

AMESSE, Denver.

SEVERE ANEMIA WITH TUMOR OF THE SPLEEN AND CRANIAL CHANGES CURED AFTER REMOVAL OF A FECAL TUMOR IN THE RECTUM. J. CATHALA and P. MOREL, Nourrisson **26**:147 (May) 1938.

A boy was born prematurely, the mother having been pregnant for seven months. At the age of 2½ years he had a large tumor of the spleen. The hemoglobin percentage was 20, and the red blood cell count was 2,500,000, of which 3 per cent were reticulocytes. The fragility test was normal. There was no jaundice. The skull changes were those found in Cooley's anemia. Under anesthesia and with the use of prostigmine and castor oil, a fecaloma twice as big as a fist was removed without operation. Rapid, continuous recovery followed.

HYMANN, Cleveland.

STUDIES ON THE SPEED OF APPEARANCE OF NEUTRAL RED IN THE GASTRIC JUICE AFTER INTRAMUSCULAR INJECTION OF THE DYE INTO HEALTHY INFANTS AND INTO INFANTS WITH FUNCTIONAL GASTROINTESTINAL DISTURBANCE. A. FERRO, Lattante **9**:187 (May) 1938.

The dose of neutral red injected was from 1 to 2 cc. of a 1 per cent aqueous solution. The injections were made after the infants had been without food for twelve hours.

Of 50 healthy infants from 1 to 15 months of age who were given this test, no dye was excreted by 5. In the others the dye appeared in the gastric juice between four and forty minutes after injection; the mean of greatest frequency was between eight and twelve minutes. The speed of secretion was consistently neither faster nor slower in breast-fed than in bottle-fed infants. Of 30 vomiting infants, no dye was excreted by 12; in the others the dye appeared in the gastric juice between eleven and thirty-two minutes after injection.

Although in functional vomiting gastric secretion of the dye tends to be depressed, the test was believed by Ferro to be of no practical value for the individual patient.

HIGGINS, Boston.

EXAMINATION FOR APPENDICITIS IN THE YOUNG CHILD DURING SLEEP. E. FLUSSER, Kinderärztl. Praxis **9**:188 (May) 1938.

Pains due to appendicitis are more pronounced during the night than during the day. It therefore is typical that in cases of appendicitis children, as well as their parents, have sleepless nights. If the region of McBurney is palpated while the patient is asleep (either spontaneously asleep or through administration of phenobarbital), and the patient awakens because of the pain, the observation favors a diagnosis of appendicitis. If, on the other hand, it is possible to palpate McBurney's region without awakening the patient, acute perforating appendicitis can be excluded.

HEYMANN, Cleveland.

HEREDITARY GASTROINTESTINAL PATHOLOGIC CHANGES LIMITED TO THE MALES. K. HERFORT, Časop. lék. česk. **75**:1201 (Sept. 25) 1936.

Herfort reports that 10 males in four generations of a family suffered from gastrointestinal symptoms. One died of carcinoma of the stomach; 1 had pylorospasm; 1 had duodenal ulcers; 5 had gastric ulcers, and in 2 identical twins, the youngest males of the family, there was at the time of writing a deviation in the secretion and organization of the gastric mucosa. These twins were being watched for subsequent ulcer.

STULIK, Chicago.

THE "SUMMER DIARRHEA" OF CHILDREN IN ANGORA, TURKEY. A. ECKSTEIN, Acta pædiat. **20**:431, 1938.

This long, detailed report deals with 700 cases of summer diarrhea observed during the year 1936 in Angora, the contemporary capital of Turkey, a city of 122,720 persons, according to the census of 1935. The majority of infants in this community are breast fed during the entire first year of life and many well into the second year. However, breast feeding appeared to offer little or no protection against the disease. The first cases occurred during May, a cool month, and the decline of new cases took place during August, at the peak of the hot season. "Toxicosis" was the rule; "exsiccosis" was uncommon; a tendency toward edema was observed frequently. Bacteriologic examination of the stools revealed typhoid or dysentery organisms in only a few instances. Agglutination tests of the blood serum in 185 cases yielded a diagnostically significant Widal phenomenon in only 17 per cent of the cases. This paucity of evidence of infection by the usual intes-

tinal pathogenic micro-organisms led the author to suspect the presence of some infectional agent that was not isolated, a toxin-producing colon bacillus, for example.

Dysentery antiserum appeared to be of definite therapeutic benefit; that this effect was nonspecific was made clear when equally satisfactory results were obtained with normal serum. Cardiac stimulants and restriction of the diet were also advantageous. Since breast feeding alone appeared to offer little immunity from infection, the author advises that general hygienic measures be scrupulously practiced in order to prevent similar outbreaks. The bibliography is brief.

McCune, New York.

Celiac Disease. G. Fanconi, Maandschr. v. kindergeneesk. **7**:135 (Jan.) 1938.

This article represents a discourse by the Swiss pediatrician in November 1937 in universities in the Netherlands. Special stress is laid on the therapy used in Zurich, Switzerland, consisting chiefly in a diet of bananas and acid milk.

van Creveld, Amsterdam, Netherlands.

Nervous Diseases

Dystonia Musculorum Deformans: A Clinicopathologic Study. C. Davison and S. P. Goodhart, Arch. Neurol. & Psychiat. **39**:939 (May) 1938.

The authors report a detailed clinical and pathologic study of torsion dystonia. They specially point out that the main lesions were in the putamen, caudate nucleus and dentate nucleus.

Beverly, Chicago.

Reduction of Increased Intracranial Pressure by Concentrated Solutions of Human Lyophile Serum. J. Hughes, S. Mudd and E. A. Strecker, Arch. Neurol. & Psychiat. **39**:1277 (June) 1938.

Lyophile serum is concentrated human blood serum. The serum in a frozen state is dried in a high vacuum. Sufficient water or 50 per cent sucrose is added to produce a concentration of four times normal. The term "50 cc. of serum of four times normal concentration in a 50 per cent solution of sucrose" indicates that the solids of 200 cc. of serum have been dissolved in a 50 per cent solution of sucrose to make a vial of 50 cc.

Such serum is theoretically of value because of the normal impermeability of the blood capillaries in man to serum proteins. It is given intravenously up to 200 cc. at a time. It reduces intracranial pressure for much longer periods than 50 per cent sucrose alone or other hypertonic solutions.

Beverly, Chicago.

Moro Reflex and Startle Pattern. K. Goldstein, C. Landis, W. A. Hunt and F. M. Clarke, Arch. Neurol. & Psychiat. **40**:322 (Aug.) 1938.

The Moro reflex is obtained in young infants and gives way to the startle pattern. The two may be seen together between 6 weeks and 4 months of age. At the latter age the Moro reflex completely disappears. There are two parts to the Moro response. In the first part there is stretching of the trunk, the head is tilted backward, and there are abduction and extension of the arms and extension of the hands. In the second part the arms are flexed and brought together before the chest. There is an interval between the two responses. Genetically, the second part disappears first. The authors suggest that the second part, which has been called the clasping response, may be but a return of the extremities to the resting position. They consider it erroneous to refer to the reflex as an adaptive, protective clasping response.

The startle pattern consists in closing the eyes, moving the head, raising and bringing together the shoulders, abducting the lower part of the arm, clenching the fist, moving the trunk forward, contracting the abdomen and bending the knees.

The authors studied the responses by the use of an ultrarapid photographic machine.

BEVERLY, Chicago.

FAT IN THE INFANT BRAIN IN RELATION TO MYELIN, BLOOD VESSELS AND GLIA. C. R. TUTHILL, Arch. Path. **25**:336 (March) 1938.

This is a contribution to the argument, beginning with the studies of Virchow, concerning the pathologic versus the physiologic nature of the fat found in the glia cells of the white matter of the newly born infant's brain. Forty-six brains were examined. Twenty-five were from infants less than 6 months old, and the others were from infants of various ages up to 2 years. Tissues were removed from the occipital lobe, the frontal and central parts of the cortex and the midportion of the cerebellum. Fat was found around the blood vessels and glia cells of the centrum ovale, corpus callosum and white substance of the lower part of the gyri in all of 21 infants less than 4 months of age. The fat decreases with the formation of myelin and ceases at the age of 4 months. Tuthill concludes that the fat is a waste product of myelin metabolism and occurs chiefly in areas of poor capillary circulation.

APFELBACH, Chicago.

ADIPOSITY AND DIABETES MELLITUS IN A MONKEY WITH HYPOTHALAMIC LESIONS. S. W. RANSON, C. FISHER and W. R. INGRAM, Endocrinology **23**:175 (Aug.) 1938.

In a monkey in which lesions had been induced in the hypothalamus adiposity developed within three weeks. At autopsy normal mature testes were found, and there was some evidence that premature descent of the testes may have occurred. There had also been diabetes mellitus, which was explained by the finding in the pancreas of hydropic degeneration of the isles of Langerhans. The lesions in the hypothalamus and the histologic character of the hypophysis, adrenal glands and thyroid were studied without discovering clear evidence of the cause of the adiposity.

JACOBSEN, Buffalo.

STREPTOCOCCUS MENINGITIS. A. R. EVELOFF, Illinois M. J. **74**:162 (Aug.) 1938.

Eveloff reports the recovery of a child from postscarlatinal mastoiditis, complicated by an infection with Streptococcus meningitis, following treatment with sulfanilamide. No surgical treatment was resorted to.

BARBOUR, Peoria, Ill.

CARE AND TREATMENT OF CEREBRAL PALSIES. W. M. PHELPS, J. A. M. A. **111**:1 (July 2) 1938.

In determining a handicapped child's mental age, the effect of the handicap should be remembered, and it may be necessary to observe his learning power over a period of time. It is fundamental to treatment to determine the type of palsy, whether spastic or athetoid. Repetitive methods are of definite use for spasticity, while relaxation is the keynote for the athetoid child. The plan of training should be determined with a view to the child's greatest need. Training in certain activities should be directed to their proper relation in time and the muscle groups studied to arrive at the best method of coordination. Surgical treatment may be indicated for the child who is spastic.

Adequate care and treatment are complicated and demand extensive and various investigations.

HEERSMA, Kalamazoo, Mich.

INFANTILE CEREBRAL PALSY (SPASTIC PARALYSIS): A DISCUSSION ON THE ETIOLOGY. C. H. HEYMAN, J. A. M. A. **111**:493 (Aug. 6) 1938.

Experience with palsy in a thousand children in an orthopedic clinic aided the author to analyze the causes. He believes the term "Little's disease" is misused and should be deleted, since it probably describes a condition of a different clinical and etiologic nature.

The location of the paralysis indicates somewhat its origin. Asymmetric lesions are produced by some factor operating before birth. Other etiologic factors discussed are neuropathic heredity, primary brain defect, infections, prematurity, hemorrhagic disease and accidents incident to birth.

HEERSMA, Kalamazoo, Mich.

EFFECT OF SIMULTANEOUS INOCULATION WITH VARIOUS MICRO-ORGANISMS ON THE PATHOGENESIS OF ST. LOUIS ENCEPHALITIS IN MICE. E. A. COOK, J. Infect. Dis. **63**:127 (July-Aug.) 1938.

Various bacteria and bacterial toxins and two viruses, that of human and that of swine influenza, were found incapable of altering the genesis of St. Louis encephalitis in mice when sprayed together with the St. Louis virus in the nasal passages of these animals.

TOOMEY, Cleveland.

RESPONSE OF SPECIFICALLY IMMUNIZED MICE TO REINOCULATION WITH VIRUS OF ST. LOUIS ENCEPHALITIS, WITH ESPECIAL ATTENTION TO THE DEVELOPMENT OF MYELITIC SYMPTOMS. E. A. COOK, J. Infect. Dis. **63**:206 (Sept.-Oct.) 1938.

Intracerebral or intranasal reinoculation of mice from seven to twenty-one days after one or two previous injections of the virus of St. Louis encephalitis by either the subcutaneous or the intraperitoneal route may give rise to sudden flaccid paralysis of the limbs, with a fatal or a nonfatal outcome. Similar results may be obtained by intracerebral reinoculation of mice after one or two previous intranasal inoculations.

The incubation period of the paralytic condition is from five to fourteen days, being shorter (from five to eleven days) after intracerebral than after intranasal injection (from eleven to fourteen days).

Suspensions of the brains or spinal cords of such paralyzed animals when injected into normal mice give rise to typical encephalitis. Virus in the cord usually has a slightly higher relative titer than that in the brain, but in both instances the titer is comparatively low and the virus disappears rapidly.

The localization of the paralytic symptoms is not correlated with the site of injection, and virus is not detectable in the central nervous system seven, fourteen or twenty-one days after the injection of a nonlethal dose.

The serum of mice given a single subcutaneous or intranasal nonlethal injection of virus possesses little or no neutralizing capacity. However, a certain degree of immunity is shown to exist in animals so treated by their resistance to subsequent inoculations of virus rapidly lethal to controls.

The chief pathologic changes in the spinal cords of paralyzed mice are vascular congestion, perivascular and diffuse round cell infiltration, proliferation of microglia and nerve cell degeneration, especially in the anterior horns.

TOOMEY, Cleveland.

DIAGNOSIS OF MENINGITIS IN THE NEWBORN AND INFANT PERIODS. M. COOPERSTOCK, J. Michigan M. Soc. **37**:698 (Aug.) 1938.

Cooperstock points out that the etiologic factors of meningitis in this age group differ from those of meningitis in older children and adults. The clinical picture of meningitis is generally absent, and initial symptoms are lacking. The

most helpful symptoms in early diagnosis are convulsions and bulging of the anterior fontanel. A high fever is usually present, though not always, and marked leukocytosis in the absence of fever is of significance.

Seven case histories are reviewed briefly.

It appears that in many cases of unexplained fever an examination of the spinal fluid may give a proper diagnosis.

CAREY, Detroit.

FOLLOW-UP REPORT OF NINETY-NINE CHILDREN WHO RECEIVED FEVER THERAPY FOR CHOREA. L. P. SUTTON and K. G. DODGE, J. Pediat. **12**:490 (April) 1938.

Sutton and Dodge present a follow-up study of 99 children who had been given fever therapy in their first attacks of chorea and in most of their subsequent attacks. The results were compared with those obtained on 60 children who did not receive this treatment. The subjects are divided into two groups. The first group is composed of 48 treated and 23 untreated patients observed from one

Results of Follow-Up Study and Comparison of patients with Chorea Who Were Given Fever Therapy

Condition Noted	Percentage Showing Condition: Treated Patients	Percentage Showing Condition: Controls (Untreated Patients)
Group observed from 1 to 3 years		
Chorea	31.5	37.5
Polyarthritis	6.0	32.0
Heart disease	12.5	26.0
Death from heart disease	2.8	13.0
Group observed from 4 to 6 years		
Chorea	41.0	51.0
Polyarthritis	6.0	33.0
Heart disease	29.4	35.0
Death from heart disease	1.96	10.8

to three years. The second group contains 51 treated and 37 untreated patients observed from four to six years. The comparisons showed a very much higher percentage of polyarthritis and death from heart disease among the untreated patients in both groups.

RAUH, Cincinnati.

RELATION OF POTASSIUM TO FAMILY PERIODIC PARALYSIS. G. D. GAMMON, Proc. Soc. Exper. Biol. & Med. **38**:923 (June) 1938.

A definite lowering of the serum potassium (from 25 to 30 per cent) was found in a 16 year old boy suffering from familial periodic paralysis. Administration of potassium salts at night (4 Gm. at 2:30 a. m. every night) prevented the development of seizures or made them much less frequent and severe. An attack which had already developed could be cured by oral administration of 4 Gm. of potassium chloride.

HANSEN, Minneapolis.

AN UNUSUAL EXAMPLE OF HEMIPLEGIA, A. MAITLAND-JONES, Proc. Roy. Soc. Med. **31**:760 (May) 1938.

A boy 1½ years old was admitted to the hospital with left-sided hemiplegia. Two days before admission he fell back unconscious while being dressed, vomited shortly afterward and remained unconscious for twelve hours. The following day the mother noticed conjugate deviation of his eyes to the right and stiffness of the left arm. On admission the boy was drowsy and irritable. He had two bruises on the face, one on the right thigh and one on an internal malleolus.

There was a small subconjunctival hemorrhage on the right. There was weakness of the left arm and leg, with some spasticity, and all jerks were active. The abdominal reflex was absent on the left. Two days later the child became semicomatose, with stertorous breathing and flushed face. There was complete left-sided hemiplegia. He remained in this condition for two days, after which he made a gradual but steady recovery. An account of the pathologic investigations accompanies the report.

WILLIAMSON, New Orleans.

DUMB-BELL TUMOR: DEEP X-RAY THERAPY–SCOLIOSIS. A. W. FRANKLIN, Proc. Roy. Soc. Med. **31**:766 (May) 1938.

A girl of 11½ years was admitted to the hospital in 1933 on account of ataxia and obesity. She contracted scarlet fever almost immediately and was sent to a hospital for patients with fevers. On her return the muscles of the lower extremities, back and abdomen were completely paralyzed. The legs were spastic and the tendon reflexes increased. Loss of sensation to superficial pain, heat, cold and deep pain was complete to the level of the xiphoid cartilage and partial above that level to the nipples. Lumbar puncture yielded a normal fluid, and the Wassermann reaction was negative. About this time signs of consolidation in the upper part of the left side of the chest were noted. A diagnosis was then made of compression of the spinal cord at the level of the fifth thoracic segment, probably in association with an intrathoracic tumor. A laminectomy of the first to the sixth thoracic vertebrae showed a whitish tumor overlying the spinal cord. This was too vascular to be removed by excision. As much as possible was removed by diathermy. On microscopic examination a tentative diagnosis of fibrosarcoma was made. After operation the patient quickly recovered the use of the muscles of her legs and back. Later, treatment with roentgen rays of high voltage was instituted. Two courses were given, and the child recovered completely except that the tendon reflexes are rather brisk. For the past three years there have been increasing distortion of the chest due apparently to scoliosis of the thoracic vertebrae. It is suggested that this may be due to the roentgen therapy rather than to the operation or to the tumor.

WILLIAMSON, New Orleans.

CLINICAL CONSIDERATIONS ON THREE CASES OF ACUTE CEREBRAL TREMOR IN INFANTS. R. CANNATA, Méd. inf. **9**:173 (June) 1938.

Between four and nine days after attacks of bronchopneumonia, 3 children, 15 months, 6 months and 10 months of age, began to have marked tremor and spasticity of the extremities. In from twenty-four to forty-five days recovery was complete. In 2 of the children there were recurrences of the tremor.

The lesions were probably in the cerebellar tracts, the midbrain and the basal ganglions. The injurious agent was probably a virus, the patients being carriers of the virus; the pneumonia was responsible for diminished resistance, and encephalitis ensued.

HIGGINS, Boston.

PROGNOSIS AND TREATMENT OF CHILDHOOD ECLAMPSIA. T. COMBY, Progrès méd., March 12, 1938, p. 387.

Under this heading Comby considers generalized convulsions occurring in the course of acute infectious diseases and acute hemorrhagic nephritis. The prognosis for complete recovery in both conditions is excellent. For the convulsions occurring with fever Comby recommends tepid baths and sponging and enemas of tepid water. For those occurring in acute nephritis he recommends venous section with removal of from 200 to 300 cc. of blood, scarification in the region of the kidneys and enemas of sodium sulfate.

LESLIE, Evanston, Ill.

CHARACTER OF THE MOTIONS OF EARLY CHILDHOOD. GUINDES, Rev. méd.-sociale de l'enf. **5**:355 (Sept.-Oct.) 1937.

Guindes stresses the fact that near the two extremes of life movements are very different and are governed by different mechanisms. During the first few weeks and months of an infant's existence its motions are determined purely by reflex and its muscular ability. Later in life reflex and muscle power play a much smaller part; habit and thought guide most motion. The athetoid character of many early action patterns is stressed, and the frequency of apparently involuntary motion of voluntary muscles is mentioned. Infantile movement is essentially pluriarticular; mature movement is frequently monoarticular. In infancy the various motions are largely dependent on age; in adult life they are dependent on the man and his personality.

DIETRICH, Beverly Hills, Calif.

JUVENILE AMAUROTIC IDIOCY (SPIELMEYER-VOGT TYPE). M. DIDE and L. VAN BOGAERT, Rev. neurol. **69**:1 (Jan.) 1938.

Dide and van Bogaert present a case of this rare syndrome, with the results of extensive histologic studies, and arguments as to classification. The syndrome appears in childhood. It is characterized by epilepsy, progressive idiocy, loss of vision, optic atrophy and motor disturbances similar to parkinsonism. There is a familial tendency; it tends to occur in Aryan families linked by consanguinity. There is usually a tuberculous background. The degenerative lesions are most marked in the neostriatum, the optic thalamus, the cerebellum and the anterior horns of the cord. The Purkinje cells disappear. There seems to be a selectivity for the ganglion cells, while the mesodermal derivatives are spared. There is considerable lipoidosis, remarkably similar to that occurring in old age, which the authors consider due to progressive cellular intoxication.

DAFFINEE, Boston.

A CASE OF FOERSTER'S DISEASE (AMYOTONIC ENCEPHALOPATHY). A. BORGES-FORTES, Arch. de pediat., Rio de Janeiro **10**:491 (July) 1938.

The case presented is that of a 2 year old boy with the condition named (paradoxic muscular tonus with origin probably in some disturbance of the labyrinth).

SANFORD, Chicago.

INFANTILE CONVULSIONS. A. G. ALARCON, Rev. mex. de puericultura **7**:447 (Sept.) 1937.

Alarcon divides infantile convulsions into two groups: those of known cause and those of obscure or unknown cause, which he calls idiopathic. He mentions the various known causes of convulsions in infancy and discusses the mechanism of these nervous phenomena. He does not believe dentition is a cause of convulsions. He reviews the etiologic factors and comments briefly on each.

HERRON, Monroe, La.

MEDULLOBLASTOMA WITH THE SYNDROME ADIPOSOGENITALIS DYSTROPHIA. M. FUENTES, Rev. mex. de puericultura **8**:199 (April) 1938.

Fuentes reviews the general classification of tumors of the brain and presents a case of medulloblastoma in a 13 year old boy, who also presented the syndrome adiposogenitalis dystrophia. Ventriculograms show the enlarged ventricles. He presents in detail the history, the physical findings, the changes noted at autopsy, the laboratory data and the roentgen observations.

HERRON, Monroe, La.

TREATMENT OF SYDENHAM'S CHOREA WITH FEVER THERAPY. M. F. BLANCO, Rev. mex. de puericultura **8**:223 (April) 1938.

Blanco discusses the history, causes, symptoms, course and general treatment of chorea. He then reports the results of fever therapy in 3 cases and, as would be expected, does not draw conclusions.

HERRON, Monroe, La.

TRYPTOPHAN TEST IN TUBERCULOUS MENINGITIS. D. N. BOBEFF, Monatschr. f. Kinderh. **73**:358 (June) 1938.

The tryptophan test is 100 per cent efficient. In over 70 cases it was of extreme value in differentiating tuberculous meningitis from other types of disease of the central nervous system.

GERSTLEY, Chicago.

TREATMENT OF SPASTIC TORTICOLLIS. G. SCHALTENBRAND, Deutsche Ztschr. f. Nervenh. **145**:36, 1938.

Schaltenbrand reports 13 cases of spastic torticollis in adults. In 2 cases the disturbance occurred in a father and a daughter and was classified as a manifestation of a hereditary extrapyramidal disease. In 2, possibly 3, the disease was postencephalitic. In a fourth case the torticollis occurred in a patient 67 years of age with evidence of cerebral arteriosclerosis and was of one year's duration. In 7 cases no cause for the disease was found. In the majority of the cases myographic examination showed disturbance in the innervation of the musculature of the arms and sometimes in that of the legs, also. These disturbances did not disappear after operation. In 4 cases in which the entire musculature of the neck was infiltrated with procaine hydrochloride the spastic attacks ceased for at least twenty-four hours. In 4 cases a 0.5 per cent solution of procaine hydrochloride was given by injection for several weeks. In a single case sixty injections of procaine and alcohol were given in nineteen treatments in four months. In all cases in which adequate use of procaine was made the patients were practically cured and were able to return to their professions. Because of its lack of danger, the author suggests that this treatment be employed before a more radical operation is undertaken. He points out that in cases of progressive encephalitis of hereditary origin the disease does not respond to this kind of treatment but requires operation.

ADLER, Boston. [ARCH. NEUROL. & PSYCHIAT.]

CLINICAL AND ANATOMIC STUDIES IN A CASE OF CHOREA MINOR. G. G. NOTO, Ztschr. f. d. ges. Neurol. u. Psychiat. **159**:781 (Sept.) 1937.

Noto reports the case of a woman aged 60 who on Dec. 3, 1933, felt feverish and the next day complained of pains in the joints. She was treated with salicylates for a few weeks. After a few days dyspnea, tachycardia and mitral insufficiency were found. At the same time she had bilirubinuria and hyperbilirubinemia. Toward the end of February 1934, she began to show choreic movements on the left side. The clinical picture was definitely that of chorea. The movements continued to be most marked on the left side and were less marked in the lower limbs; they ceased during sleep and were worse during emotional upsets. The tongue was involved in the movements. The muscular power was weakened throughout. There was bilateral dysdiadokokinesis. The deep reflexes were depressed. The pupils reacted sluggishly to light and somewhat better in accommodation. Serologic tests of the spinal fluid gave negative results. The mastic curve was normal. The patient died on May 2, in status choreicus. Autopsy showed: recent endocarditis, with infiltration of the cardiac muscle and Aschoff bodies; hyperemia of the meningeal and cerebral vessels but no perivascular infiltration; diffuse changes in the ganglion cells, involving especially the cells of the cerebral cortex and cerebellum, with tigrolysis, pyknosis and pigmentary and vacuolar degeneration. No significant changes were seen in the walls of the blood vessels.

Noto stresses the advanced age of this patient with rheumatic fever and chorea minor. Anatomically, the absence of evidence of inflammation was noteworthy. Noto adds that this may be correlated with the relatively long duration of the illness. The diffuse changes in the ganglion cells were the only pathologic observations in the brain. The basal ganglions were not especially involved.

SAVITSKY, New York. [ARCH. NEUROL. & PSYCHIAT.]

FURTHER INVESTIGATIONS INTO THE DIASTASE CONTENT OF THE VENTRICULOSUBARACHNOID SPACE. H. CHRISTIANSEN, Acta psychiat. et neurol. **12**:599, 1937.

Christiansen has shown that in 80 per cent of cases studied by him the diastase content of the cerebrospinal fluid represented from 1 to 5 per cent of that of the blood serum. In only 2 per cent of cases was the diastase content less than 1 per cent of that of the blood serum. In the present study he reports the results of determinations of diastase in the cisternal, lumbar and ventricular fluids. Simultaneous determinations of diastase in the blood serum and in the cisternal and lumbar fluids of 2 alcoholic patients showed that the cisternal fluid contained slightly less diastase than the lumbar fluid. The results of the determinations of diastase in 35 samples of ventricular fluid show that the ratio of diastase in the serum to that in the ventricular fluid is less than 1:100. Also, the absolute concentration of diastase is low. The diastase content of the cerebrospinal fluid increases caudally. This is explained by the fact that diastase is composed of large molecules, approaching in size the molecules of protein. Thus, its concentration in the ventriculosubarachnoid fluid is similar to that of proteins.

YAKOVLEV, Waltham, Mass. [ARCH. NEUROL. & PSYCHIAT.]

A CASE OF SYMMETRIC GANGRENE WITH INCREASE OF THE INTRACRANIAL PRESSURE. E. GORTER and H. BROEKEMA, Maandschr. v. kindergeneesk. **7**: 315 (May) 1938.

A boy 2½ years old fell ill without any clear etiologic explanation for the condition, which was manifested in symmetric cyanosis and partial necrosis of the feet, hypertension and slight albuminuria. The cyanosis soon disappeared, but focal nephritis developed, with increase of intracranial pressure, which was combated by means of repeated lumbar punctures. The fundus oculi showed a congested papilla; the spinal fluid showed nothing abnormal. The excretion of phenol red in the spinal fluid was insufficient, though the renal function was normal. The blood showed striking eosinophilia. The authors are inclined to accept the explanation that a cerebral lesion was the cause of the symmetric gangrene and of the increased intracranial pressure.

VAN CREVELD, Amsterdam, Netherlands.

CALCIBRONATE IN THE TREATMENT OF EPILEPSY. A. Q. VAN BRAAM HOUCKGEEST, Nederl. tijdschr. v. geneesk. **82**:1097 (March 5) 1938.

The author advocates a trial of calcibronate (bromion and calcium gluconate) in the treatment of epileptic persons when other measures fail to effect an improvement and illustrate this therapy with brief reports of 5 cases in which the drug was used; 3 of the patients were children, and 2 were adults.

VAN CREVELD, Amsterdam, Netherlands.

TREATMENT OF POSTENCEPHALITIC PARKINSONISM. J. C. BROEKEMA, Nederl. tijdschr. v. geneesk. **82**:3323 (July 2) 1938.

Broekema reports on the treatment of postencephalitic parkinsonism after the method of Panegrossi, i. e., by means of a special extract of the roots of Atropa belladonna. He cites some patients in whom great improvement has been obtained.

Also he states that this treatment is able to ameliorate paralysis agitans. The shorter the duration of symptoms the more favorable are the results of the treatment.

VAN CREVELD, Amsterdam, Netherlands.

INHERITANCE OF EPILEPSY. G. P. FRETS, Nederl. tijdschr. v. geneesk. **82**:3437 (July 9) 1938.

A case of hereditary epilepsy is recorded and consideration given to the knowledge of heredity as a factor in epilepsy. In the case described there was inheritance of epilepsy on the paternal side. When one assumes that the heredity is recessive, the mendelian doctrine requires one to assume the presence of the hereditary factor for epilepsy in the mother as well. The results of the more recent investigations on the inheritance of epilepsy are recorded. The figures are much lower than those for dementia praecox. Further investigations on the causes of epilepsy, including the heredity, are much needed.

VAN CREVELD, Amsterdam, Netherlands.

Psychology and Psychiatry

NEGATION OR REVERSAL OF LEGAL TESTIMONY. M. H. ERICKSON, Arch. Neurol. & Psychiat. **40**:548 (Sept.) 1938.

Erickson reports the change in attitude and memory of two sisters—9 and 11 years old—toward extremely unpleasant experiences which they suffered in their own home. They were subjected to all forms of illicit and abnormal sex practices by sadists under the supervision of their parents. When first interviewed, they both gave the same apparently true story. Several months later they both denied the story and had apparently forgotten a large proportion of the facts. They both reacted in the same way, although they had been separated in the interim. The older girl summarized the situation by saying it was "utterly intolerable, one that could be imagined but not endured." By regarding the experience as imaginable but unendurable, she could give herself free rein to regard it as imaginary, utilizing the fact of her survival as proof of its imaginary character.

BEVERLY, Chicago.

SPEECH DEFECTS IN CHILDHOOD. W. G. WYLLIE, Practitioner **141**:310 (Sept.) 1938.

Speech defects in childhood are described under the headings of delayed speech, defective speech and stammering. Many normal children are late in learning to speak, but by far the larger number of children with this defect show some degree of feeblemindedness. In infants a state of ill health is a common cause of delay in speaking and, as a matter of fact, in development in general. In many cases deafness accounts for delayed speech. In the cases in which the defect is congenital the condition may not be suspected until the child is 2 or 3 years old, as development in other directions is normal. Acquired deafness is usually the outcome of severe ear trouble or of cerebrospinal fever or of congenital syphilis.

Congenital word deafness, a form of auditory imperception, in a child of normal hearing is a rare cause of delay in speech. Word-blindness, a form of visual imperception, is a commoner condition limiting self expression by spoken language.

Several of the forms of defective speech, when persisting for longer than a short phase in development, are more likely to be found in mentally defective than in normal children. The articulation of consonants—demanding adjustments of the lips, palate and tongue—is always more difficult to acquire than that of vowels, which are produced mainly in the pharynx.

Lisping, lalling, and idioglossia are minor to major defects in articulation of consonants.

The stammerer has difficulty in uttering certain letter sounds—consonants more often than vowels—and on meeting one of them, especially at the beginning of a word, "sticks silently," while the stutterer repeatedly ejaculates the difficult letter —often one of the explosive consonants, p or B—before completing the word. Stammering is far commoner than stuttering. Both are functional disorders depending on faulty coordination of three mechanisms, the lungs (or bellows), the larynx and vocal cords, and the articulatory group of the tongue, lips, palate and jaws. The compelling cause is an emotion disorganizing speech so that the natural free flow without conscious effort falls into separate components, to one of which exclusive attention should be diverted. GELSTON, San Francisco.

II. BEGINNINGS OF HUMAN PERSONALITY. M. ACQUA, Méd. inf. **9**:243 (Aug.) 1938.

This is another in a series of articles previously reviewed. This chapter discusses the concept of death and of religion, deception and imitation.

HIGGINS, Boston.

III. BEGINNINGS OF HUMAN PERSONALITY. M. ACQUA, Méd. inf. **9**:271 (Sept.) 1938.

This article concludes the series on the development of the child's personality. The attention, the will and the character are discussed. HIGGINS, Boston.

THE PSYCHOPHYSIOCHRONOMETRY AND ITS APPLICATION. L. MATA, Bol. Inst. internac. am. de protec. a la infancia **12**:5 (July) 1938.

A method of measuring the psychomotor reaction time is presented. It finds application in estimations of individual characteristics of efficiency.

LESLIE, Evanston, Ill.

Diseases of the Genitourinary Tract

EMBRYOMA OF THE KIDNEY (WILM'S TUMOR). W. E. LADD, Ann. Surg. **108**: 885 (Nov.) 1938.

Embryoma of the kidney is one of the most malignant growths of early life, the patients showing a very high mortality. The tumor is a large grayish white solid mass, probably of congenital origin. It is surrounded by a dense connective tissue capsule, which is continuous with that of the kidney. Usually the tumor cannot be freed from the kidney. It is characterized by (1) a variegated histologic structure; (2) rapid growth after a period of lower activity; (3) common occurrence of hemorrhage and necrosis, which may lead to rupture of the capsule; (4) a possibility of invasion of the renal vein or of the pelvis of the kidney; (5) a tendency to reach a large size before metastasis occur; (6) frequency of local recurrence and metastasis to the regional lymph nodes or remote metastasis through the blood stream to the lungs.

The age incidence of embryoma of the kidney is a great help in diagnosis. In the author's series of 45 cases the average age of incidence was 2 years and 3 months. The youngest patient was 2 months and the oldest 7 years of age. The parent usually brings the child to the physician because of an increase in the size of the child's abdomen. It is common for the child's general health to appear very good in spite of the large tumor.

Aspiration biopsy is not recommended, being considered unreliable as a diagnostic method, unsafe as a surgical procedure and likely to cause recurrence by implantation.

The routine treatment as employed in many clinics is preoperative irradiation for the purpose of shrinking the tumor, followed by nephrectomy, which is followed by postoperative irradiation. The author favors immediate nephrectomy without irradiation and is uncertain of the value of postoperative roentgenotherapy.

The author gives his operative technic in detail.

BANTIN, Omaha.

URINARY CHANGES DUE TO SULFANILAMIDE ADMINISTRATION. M. B. STRAUSS and H. SOUTHWORTH, Bull. Johns Hopkins Hosp. **63**:41 (July) 1938.

In 3 normal human subjects, the administration of sulfanilamide was accompanied by a decrease in the carbon dioxide–combining capacity of the plasma, definite diuresis and an increase in the renal excretion of sodium and potassium.

Two dogs showed slight losses of base through renal excretion but not enough to alter the carbon dioxide–combining capacity of the plasma, even though they received larger doses of sulfanilamide per kilogram of body weight than did the human beings.

FROM THE AUTHORS' SUMMARY.

CONCENTRATED HUMAN BLOOD SERUM AS A DIURETIC IN THE TREATMENT OF NEPHROSIS: A PRELIMINARY REPORT. C. A. ALDRICH, J. STOKES JR., W. P. KILLINGSWORTH and A. C. MCGUINNESS, J. A. M. A. **111**:129 (July 9) 1938.

The authors discuss theoretic considerations concerning the treatment of nephrosis. To replace the protein lost from the blood a concentrated (lyophile) serum was used in the treatment of 9 patients, 6 of whom showed immediate complete diuresis and 4 of whom had normal urine shortly. The case histories are given.

HEERSMA, Kalamazoo, Mich.

AMYLOID DISEASE AND THE CONGO RED TEST. P. CANTONNET, H. LIEUTIER, H. CANTONNET and W. AYALA, Arch. de pediat. d. Uruguay **9**:289 (May) 1938.

The authors report the case of a 13 year old boy with Pott's disease, marked cachexia and symptoms of renal involvement. A diagnosis of amyloid disease was confirmed by the congo red test. The main manifestations were albuminuria, cholesteremia, hypoproteinemia and enlargement of the liver and spleen without edema.

SCHLUTZ, Chicago.

RENAL DWARFISM. A. LOESCHKE, Jahrb. f. Kinderh. **147**:65 (July) 1936.

Loeschke presents several case histories of renal dwarfism in children. One child presented gigantism associated with bilateral hydronephrosis and urinary findings characteristic of nephritis and infection of the urinary tract. This condition is classified by the author as renal gigantism.

LANDAU, Hannibal, Mo.

HYDRONEPHROSIS ASSOCIATED WITH CONGENITAL DISLOCATION OF THE HIP IN AN INFANT OF FOUR MONTHS. V. KAFKA JR., Časop. lék. česk. **75**:1371 (Oct. 30) 1938.

Kafka reports the case of an infant of 4 months, a girl, with congenital hydronephrosis on the left. The kidney was represented by a large unicellular cyst with merely a thin layer of renal tissue. The etiologic explanation was based on complete atresia of the ureter from the pelvis of the kidney to the bladder terminus, where a diverticulum formed. Recovery took place after nephrectomy. The associated congenital dislocation of the right hip was corrected at the age of 18 months. The child was watched for six years after the nephrectomy, and no complication was noted.

STULIK, Chicago.

A Method for Direct Staining of Erythrocytes in the Wet Urine Deposit. A. W. Endtz, Nederl. tijdschr. v. geneesk. **82**:856 (Feb. 19) 1938.

Endtz describes a benzidine method for direct coloring of red blood corpuscles in the wet urine deposit, which makes the detection of erythrocytes in urine much easier and excludes mistakes. In addition, a staining method is devised which enables one to differentiate erythrocytes, small and large lymphocytes and polymorphonuclears in the urinary deposit.

van Creveld, Amsterdam, Netherlands.

Treatment of Hypospadias. R. J. Harrenstein, Nederl. tijdschr. v. geneesk. **82**:2963 (June 11) 1938.

Harrenstein considers the various forms of hypospadias and points out the difficulties of treating them, also the difficulties connected with choosing among many methods of operation. He uses the methods of Beck and Duplay. He discusses some of the technical details and draws attention to mistakes which might lead to failure. He describes and illustrates a means he uses for the fixation of the penis during operation. He reports the results obtained in 9 patients and discusses the closing of the fistulas that almost inevitably follow the operation.

van Creveld, Amsterdam, Netherlands.

Diseases of the Ductless Glands; Endocrinology

Gonadotropic Action of Normal Male Urine Extract on the Dog. J. H. Leathem and J. A. Morrell, Endocrinology **23**:164 (Aug.) 1938.

An extract of normal male urine was found comparable to an extract of menopausal urine in inducing estrous reactions in 11 of 12 normal dogs tested.

Jacobsen, Buffalo.

Effect of Castrate Urine Hormone on the Testis. H. S. Rubinstein, Endocrinology **23**:171 (Aug.) 1938.

A follicle-stimulating substance obtained from the blood and urine of women who have passed the menopause and from the blood and urine of castrates induces premature testicular descent in normal immature albino rats.

Although the proliferation of germinal cells is increased, maturation is not hastened. The follicle-stimulating factor has no effect on general body growth.

Jacobsen, Buffalo.

Histologic Effects Induced in the Anterior Pituitary of the Rat by Prolonged Injection of Estrin with Particular Reference to the Production of Pituitary Adenomata. J. M. Wolfe and A. W. Wright, Endocrinology **23**:200 (Aug.) 1938.

A study was made of the pituitaries of 37 rats receiving injections of an estrogenic substance for periods of from thirty to four hundred and twenty-five days. In rats treated for the shorter periods marked but uniform hypertrophy of the gland was induced, but in rats treated for prolonged periods adenomas were induced.

Jacobsen, Buffalo.

Fatty Atrophy Following Insulin Injection in Nondiabetic Malnutrition. H. Blotner, Endocrinology **23**:233 (Aug.) 1938.

This paper presents some observations on local atrophy of fat in a normal thin person who took insulin for three weeks to gain weight. About four or five

months after she ceased taking the drug, the atrophy was noted in the right thigh, where the drug had been injected twice as frequently as in the left thigh. The area involved increased in size and reached its maximal diameter of 6 cm. and its maximal depth of 0.9 cm. in the subsequent four months. During the past two and a half years the depression in the thigh has remained stationary except during pregnancy, when it appeared more marked. Over the region of the atrophy sensation is diminished. This case indicates that a patient does not have to be diabetic or fat to have atrophy develop after injections of insulin and that the atrophy may appear some months after the withdrawal of insulin.

JACOBSEN, Buffalo.

INFLUENCE OF ADRENAL CORTEX EXTRACT UPON COMPENSATORY HYPERTROPHY OF THE ADRENAL CORTEX. E. M. MACKAY and L. L. MACKAY, Endocrinology **23**:237 (Aug.) 1938.

When one adrenal gland is removed, the cortex of the remaining gland undergoes compensatory hypertrophy. By administering an extract of adrenal cortex this compensatory hypertrophy can be suppressed or prevented. The hypertrophy is probably dependent on stimulation by an anterior pituitary hormone the production of which depends on the concentration of an adrenal cortex hormone circulating in the organism. When, following unilateral adrenalectomy, there is a lack of the latter factor, compensatory hypertrophy of the remaining adrenal gland does not ensue if the stimulation by the anterior pituitary hormone is prevented by supplying the deficiency in cortical hormone from outside sources.

JACOBSEN, Buffalo.

INNERVATION OF THE HYPOPHYSIS. A. T. RASMUSSEN, Endocrinology **23**:263 (Sept.) 1938.

Forty-eight human hypophyses were submitted to careful histologic examination to obtain data on their innervation. Rasmussen describes the results.

JACOBSEN, Buffalo.

HYPERTROPHY OF THE THYMUS IN AN INFANT CURED BY ROENTGEN RAYS. C. HURMUZACHE and S. PINELES, Bull. Soc. de pédiat. de Iasi **8**:12 (Jan.-June) 1937.

This article is accompanied by roentgenograms showing the condition before and after treatment.

LESLIE, Evanston, Ill.

THYMIC DEATH. C. MAGI, Lattante **9**:372 (Sept.) 1938.

A 64 day old girl died suddenly; there were no convulsions, no signs of suffocation, no cough, no laryngeal stridor. Thymic death was diagnosed clinically, and an autopsy was performed. The thymus was large, weighing 36 Gm., and contained cysts filled with a milklike fluid. Cultures of the thymus were negative. No other abnormality was found except some microscopic peculiarities of the thyroid and of the adrenal cortex.

HIGGINS, Boston.

LAWRENCE-BEIDL SYNDROME. L. BERLANGA BERUMEN, Rev. mex. de puericultura **7**:520 (Oct.) 1937.

The author presented, on July 23, 1936, the first case of the Lawrence-Biedl syndrome diagnosed in Mexico. He reviews the bibliography and then reports in detail this case, including the roentgen observations.

HERRON, Monroe, La.

Diseases of the Muscles, Bones, Joints and Lymph Glands

FUNCTIONAL SIGNIFICANCE OF THE LYMPHATIC SYSTEM. C. K. DRINKER, Bull. New York Acad. Med. **14**:231 (May) 1938.

The anatomy and physiology of the lymphatic system are discussed in detail. Emphasis is placed on the clinical features of this important system, especially from the point of view of its relative importance in infections. Experimental data illustrate the necessity of comprehending the significance of lymphatic obstruction as an aid to intelligent treatment of the dangerous complications involving such obstruction.

JAHR, Omaha.

BILATERAL HYDROARTHROSIS OF THE KNEES. R. A. MILLER, Proc. Roy. Soc. Med. **31**:774 (May) 1938.

A girl aged 5 years was admitted to the hospital with a history of swelling of both knees for nine weeks. There was no pain but discomfort on flexing the knees. She had just got over an illness suggestive of dysentery. The mother's Wassermann reaction was positive. The child showed no stigmas of congenital syphilis, but the liver and spleen were enlarged. The child's Wassermann reaction was found to be strongly positive. A roentgenogram of the knees showed no bony changes. After three days the child presented measles and was transfered to a hospital for patients with fever. On her return she was found to have interstitial keratitis in addition to the previous signs.

WILLIAMSON, New Orleans.

MYATONIA CONGENITALIS. I. H. ALANTAR, Arch. de méd. d. enf. **41**:458 (July) 1938.

Oppenheim's disease in a 22 month old boy is described. The patient was the youngest of 7 children and aside from one attack of pneumonia had been apparently in good health. The parents reported, however, that he was unable to sit up. On admission to the hospital, he was found in a fair state of nutrition but was pale and weak; no voluntary movements were made, and the picture was one of flaccid paralysis. The reflexes were abolished; there was marked diminution in faradic and galvanic excitability; an abnormal pliability of the joints was striking. The difficulty in differentiating such a condition from the syndrome of Werdnig-Hoffmann is pointed out by the author, who favors the view that both of these diseases are expressions of the same primary disorder.

AMESSE, Denver.

ENCHONDROPERIOSTEAL DYSTROPHY. P. NOBÉCOURT, A. HUREZ and L. BARBIER, Arch. de méd. d. enf. **41**:545 (Sept.) 1938.

The history of a case affecting a boy of 5 years is reported. The article is profusely illustrated.

While the destructive process resembled in some respects the type of achondroplasia described by Nils Silfverskiold, the fact that it attacked all the bony structures in equal degree justified the diagnosis of congenital dystrophy.

AMESSE, Denver.

POLYDYSTROPHY OF THE TYPE HURLER. J. J. BINDSCHEDLER, J. M. RODIER and HEINTZ-BERTSCH, Rev. franç. de pédiat. **14**:116, 1938.

Two cases of this peculiar type of polydystrophy occurring in the same family are described. Both patients showed all the recognized characteristics—a small stature, a large head with a high forehead, large eyes with corneal opacities, heavy eyebrows, a short trunk with marked dorsolumbar kyphosis, a large abdomen with hepatomegaly and splenomegaly, and limitation of movements. The

roentgenogram showed flattening of the epiphyses and articular surfaces, with thickening of the shafts of the long bones and sharp tapering of the distal metacarpals. The sella turcica was large. Only 22 cases of this condition have been reported. It is apparently a congenital familial disease, although there is no definite knowledge of the etiologic factors or the pathogenesis. Only a single case has come to autopsy, and in that cerebral lesions resembling those found in juvenile amaurotic idiocy were found.

LESLIE, Evanston, Ill.

HODGKIN'S DISEASE WITH PREDOMINANT SKELETAL DEVIATIONS. C. P. H. TEENSTRA, Nederl. tijdschr. v. geneesk. **82**:391 (Jan. 22) 1938.

Involvement of bone in Hodgkin's disease is not infrequent; in a few cases it precedes other symptoms. The roentgenologic picture is not characteristic; a certain diagnosis cannot be made from it. Teenstra reports on a boy of 13 years with extensive diffuse and localized skeletal changes. The findings in the spine were at first suggestive of a somewhat peculiar form of Pott's disease. The complete clinical picture of Hodgkin's disease developed eight months after the onset of backache. From then on the prevailing complex of symptoms, and after biopsy of a lymph gland the diagnosis, became evident.

VAN CREVELD, Amsterdam, Netherlands.

A CASE OF VERY PRONOUNCED RACHITIS TARDA. J. H. VAN DEN BERG, Nederl. tijdschr. v. geneesk. **82**:3202 (June 25) 1938.

Serious osteomalacia with spontaneous fractures is described in an idiot aged 18, which probably must be considered as an example of delayed rickets. A brief review of the literature is added on the connection between rickets and osteomalacia.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Eye

LYMPHOID TUMOR OF THE LACRIMAL GLAND. H. A. COOKSON and A. MACRAE, Brit. J. Ophth. **22**:385 (July) 1938.

A girl aged 9 years received a blow over the right eye, and about six months later a mass appeared in the region of the lacrimal gland. There was profound anemia, but the blood picture was at no time suggestive of leukemia. The final diagnosis was megalocytic anemia. Three months later the child died. Postmortem examination showed an enlarged spleen and an enlarged liver, small rubbery glands in the mesentery and a tumor of the lacrimal gland with a similar feel.

The lacrimal tumor was composed of masses of large and small lymphocytes lying in a delicate fibrous stroma. The cells infiltrated every portion of the tissue. There was no capsule. The specimen is compatible with lymphosarcoma or a leukemic infiltration of the lid. Sections of a gland from the abdomen showed a similar histologic structure. The authors' belief is that the growth on the lacrimal gland was a leukemic infiltration.

Illustrations accompany the article.

ZENTMAYER, Philadelphia. [ARCH. OPHTH.]

CHILDREN WITH DEFECTIVE VISION, IN NEED OR NOT OF SIGHT-SAVING CLASS. R. A. KAZ, Brit. J. Ophth. **22**:486 (Aug.) 1938.

Kaz points out that treatment directed to the cause of the reduced vision which has resulted in a child being relegated to a sight-saving class may in time bring sufficient improvement to permit the child to return to schools for normal-sighted pupils.

ZENTMAYER, Philadelphia. [ARCH. OPHTH.]

INSTRUCTION AND PROFESSIONAL ORIENTATION OF AMBLYOPIC CHILDREN: CREATION OF SPECIAL SCHOOLS. V. ORTIZ, Arch. de oftal. de Buenos Aires **13**:7 (Feb.) 1938.

In this article an appeal is made for the establishment of special schools for the education of amblyopic children. Such schools were first established in Great Britain by Bishop Harman and James Kerr. The author specifies the conditions required for admission and for the selection of the teaching personnel and the advantages to be derived therefrom.

The teaching methods are next detailed, with classification of the pupils into elementary, medium and high groups. A good general education and proper manual training are advocated, with stress on the importance of the proper selection of a profession.

FINLAY, Habana, Cuba. [ARCH. OPHTH.]

HEREDITARY ATROPHY OF THE MACULOPAPILLARY BUNDLE. R. E. GIQUEAUX, Arch. de oftal. de Buenos Aires **13**:111 (March) 1938.

Hereditary atrophy of the maculopapillary bundle in 8 members of a single family in three generations is reported. In all the members examined the defect was noticed at an early age and was coincident with slight myopia. The ophthalmoscopic picture was that of atrophy of the optic nerve limited to the temporal quadrant. The limits of the visual fields were normal, with a corresponding central scotoma. No general disease was found related to this condition. In some the disease was transmitted by the paternal, and in others by the maternal, line. The disease seems similar to Leber's hereditary atrophy in regard to involvement of both eyes and in its nonprogression after reaching its maximum; it differs in more precise central localization, in localization of the atrophy to the temporal quadrant and in its earlier appearance.

FINLAY, Habana, Cuba. [ARCH. OPHTH.]

CONTROL OF THE INTRAOCULAR PRESSURE IN INFANTILE GLAUCOMA. W. KAPUSCIŃSKI, Arch. f. Ophth. **138**:673 (May) 1938.

The object of the studies on which this paper is based was to determine in which forms or in what phases of glaucoma atropine is not contraindicated or even indicated. First, the author confirmed the well known fact that mydriatics or miotics exert no appreciable influence on the intraocular tension of normal eyes of children. In 3 patients with typical hydrophthalmos (children from 2 to 6 years of age) the tension with the use of atropine was certainly no higher than that when no medication was used or when miotics were employed. In 1 case of hydrophthalmos combined with nevus flammeus of the face pilocarpine had practically no effect, whereas the first dose of atropine after a period during which miotics were used several times produced an acute though transient drop in pressure. Still more striking was the pressure-lowering effect of atropine in a patient with glaucoma simplex (a girl aged 20) in whom it was necessary to perform cyclodialysis on each eye five times in order to bring about lasting hypotony (tension of each eye, between 8 and 13 mm. of mercury). About a year after the last cyclodialysis an acute attack of glaucoma suddenly developed in one eye, with a tension of 58 mm. of mercury and a deep anterior chamber. Pilocarpine narrowed the pupil without affecting the tension. After a dose of atropine the pupil dilated, and the tension dropped at first to 26 and a few hours later to 6 mm. of mercury. During a two months' stay in the hospital the patient had six more acute attacks, each of which was promptly controlled by the use of atropine. A striking subjective symptom which preceded each attack was a sudden lowering of the refraction caused by deepening of the anterior chamber.

KRONFELD, Peiping, China. [ARCH. OPHTH.]

CONGENITAL TORSIONAL NYSTAGMUS. J. OHM, Arch. f. Ophth. **138**:693 (May) 1938.

Seventy cases of congenital torsional nystagmus are thoroughly analyzed. Ohm's method of lever nystagmography is not suitable for the recording of pure torsion. The average visual acuity of patients with congenital torsional nystagmus is definitely better than that of patients with albinism or with colobomas of the uvea. Characteristic of congenital torsional nystagmus is relatively good vision (better than 0.5; average, 0.68) in one eye combined with relatively poor vision (average, 0.25) in the other eye. Other motor anomalies are common in cases of this condition. Strabismus occurs in 61.4 per cent; in approximately half of these cases a constant horizontal deviation is combined with a vertical component the direction and degree of which vary in the different parts of the field of fixation (oblique strabismus). The mechanism of this form of strabismus is made the subject of lengthy speculative interpretations which do not lend themselves to abstracting.

KRONFELD, Peiping, China. [ARCH. OPHTH.]

CENTRAL SCOTOMA IN CONGENITAL AND STRABISMIC AMBLYOPIA. E. HAITZ, Klin. Monatsbl. f. Augenh. **99**:761 (Dec.) 1937.

Heine proved that unilateral amblyopia without pathologic changes is usually caused by a central scotoma. He found a central scotoma in 90 per cent of the patients he examined. Uhthoff found a central scotoma in only 50 per cent of 100 patients, as he eliminated those whose vision was less than one sixth of the normal. Haitz devised a binocular stereoscopic method by which he and likewise a number of other ophthalmologists were able to show far smaller scotomas than they could demonstrate by other methods. The diameters of these scotomas varied between 2 and 6 degrees; the shape was usually round. Often the scotoma was connected with the blindspot. The paracentral scotoma was usually located temporal from, and close by, the center. The peripheral outlines of these fields were usually normal for white and colors.

STOLL, Cincinnati. [ARCH. OPHTH.]

Skin Diseases; Allergy

VITAMIN C DEFICIENCY AS A CAUSE OF URTICARIA. W. A. ROSENBERG, Arch. Dermat. & Syph. **37**:1010 (June) 1938.

Seven patients with urticaria were found to have a low level of vitamin C in the blood. The patients gave a history of low intake of vitamin C. Following addition of foods rich in vitamin C to the diet there was improvement in the urticaria and the level of vitamin C in the blood rose.

JACKSON, Iowa City.

VALUE OF IRRADIATED ERGOSTEROL IN THE TREATMENT OF ACNE VULGARIS. J. HINRICHSEN and A. C. IVY, Illinois M. J. **74**:85 (July) 1938.

The effects of viosterol (irradiated ergosterol) in the treatment of acne vulgaris were studied in 210 patients. The authors conclude that a definite and practical improvement may be obtained with daily administration of from 20,000 to 30,000 units of viosterol in about 20 per cent of patients with acne vulgaris after from two to eight weeks. Approximately 30 per cent of those who fail to show a practical improvement on this dosage will do so on 100,000 units daily. This high dosage should be accompanied by determinations of the serum calcium. The results indicate that viosterol is by no means a specific in the treatment of acne.

BARBOUR, Peoria, Ill.

DIETETIC TREATMENT OF EDEMA IN CHILDHOOD. H. FLESCH, Wien. klin. Wchnschr. **51**:689 (June 24) 1938.

Flesch, of Budapest, Hungary, notes that the causation of an edema—whether cardiac, renal or portal—is the first factor to consider in determining treatment. Besides these types of edema there is the kind which results from chronic enteritis and chronic severe dysentery, sometimes observed in older nurslings and small children. The history usually indicates that the stools have been mucilaginous, purulent and sometimes bloody. The general condition of the child is extremely bad. The pulse is weak. The heart sound is clear but hollow. There is no albumin in the urine.

At first Flesch tried "renal" therapy in such cases, giving sugared tea and fruit juices, but the condition did not improve. Attempting to get at the cause of the edema, he finally postulated an inanition of the organism due to the protracted intestinal disease and undernourishment. The resulting condition resembled the cachectic edema which is characterized as an avitaminosis.

Accordingly, a diet rich in fats and vitamins was adopted. Moro's "butter-flour mixture" and "butter–flour whole milk" were found to be especially valuable dietary aids, being palatable and sufficiently concentrated to give nourishment in small amounts. Potatoes and vegetables were then added to the diet, and gradually the pap was replaced with milk mixtures suitable for the diet at the given age. The results were generally good. Within from five to fourteen days the edema began to disappear, causing losses of weight which varied from 200 to 1,350 Gm. Then the patients began gradually to gain. The tone, turgor, color and general condition improved from day to day.

The relation of the edema to the refraction of the blood serum is interesting. Losses of weight during which the refraction index of the blood serum is subnormal indicate that the loss is from the water of the edema. Losses coincident with a normal index, however, point to destruction of tissue, and in such cases the author uses liver extract in the form of tablets or of solutions for injection and sometimes gives blood transfusions.

The Moro formulas have been widely used in feeding atrophic, dystrophic and dyspeptic infants. Their value is attributed to the proportion of fat to carbohydrate, which in the butter–flour mixture is 1 : 1.9 in the mixture of butter–flour and whole milk 1 : 1.6, while in mother's milk it is 1 : 1.7. With special reference to the edema, it is assumed that the fat in the formula has a predominant part in the cure, since it is known to bring about a reduction in the water content of tissue. Also it corrects the A avitaminosis which has caused severe disturbances in the epithelium of the intestines, leading to enteritis or dysentery. With the healing of the intestinal epithelium comes restoration of normal function, and the fat-rich diet leads to loss of the excess of water, after which the body builds up healthy new tissue.

ABT, Chicago.

Teeth and Dentistry

SUBTHYROIDISM WITH DEFECTIVE DENTAL DEVELOPMENT. C. G. KERLEY, Arch. Pediat. **55**:548 (Sept.) 1938.

Kerley reports the case of a 15 year old girl with retarded statural growth and delayed somatic development. Her height was 57 inches (144.7 cm.) and her weight 78 pounds (35.4 Kg.). Pubic hair was absent, and the mammary glands were rudimentary. The menarche had not appeared. The bone age was that of a child of 12 years.

A particularly outstanding feature of the case was the late shedding of the deciduous teeth. All the deciduous teeth but one were present in the jaws.

Desiccated thyroid, 1½ to 2½ grains (0.1 to 0.16 Gm.) daily was administered over a period of eight months. During that time the patient gained 3⅛ in. (8 cm.) in height. The menarche appeared after five months of treatment.

At the time of the first roentgen examination all the permanent teeth except the third molars were fully formed, with complete development of roots, showing

that the greatest natural eruptive force was passed and that little could be expected in the way of eruption. The second roentgen examination showed developmental changes only in the third molars. This change occurring after a period in which there was time for the stimulating effect of the thyroid therapy to be operative, suggests that if thyroid medication had been started earlier, formation and eruption of the teeth might have been satisfactory.

ORR, Buffalo.

MAXILLARY-FACIAL CELLULITIS COINCIDENT WITH THE ERUPTION OF THE FIRST DENTITION. E. HURMUZACHE and G. OSIPOV, Bull. Soc. de pédiat. de Iasi **8**:21 (Jan.-June) 1937.

Two cases are reported in which marked cellulitis with constitutional symptoms and fever preceded eruption of the second molars. In both instances, in addition to the use of hot dressings and supportive measures, surgical intervention was deemed necessary. Recovery was uneventful. The authors feel that adequate buccal hygiene would have prevented these occurrences.

LESLIE, Evanston, Ill.

Miscellaneous

"ANTIENDOTOXIC" ACTION OF CERTAIN ORGANIC SULFUR COMPOUNDS WITH REVIEW OF THE THEORIES OF THE MECHANISM OF ACTION OF THE SULFONAMIDE COMPOUNDS. P. GROSS, F. B. COOPER and M. LEWIS, J. Infect. Dis. **63**: 245 (Nov.-Dec.) 1938.

Cooper and Lewis summarize their observations as follows: "No antiendotoxic action of sulfanilamide could be demonstrated against formalin-killed meningococci in mice, against formalin-killed streptococci in mice, or guinea pigs, or heat-killed streptococci in guinea pigs. Similarly, no antiendotoxic action of 4,4′-di-(acetylamino) diphenyl-sulfone was demonstrable against formalin-killed streptococci in mice."

TOOMEY, Cleveland.

POSTGRADUATE EXTENSION COURSES IN PEDIATRICS. G. M. LYON, West Virginia M. J. **34**:352 (Aug.) 1938.

This paper was read at the conference of state directors of maternal and child health, held under the direction of the Children's Bureau, Washington, D. C., in October 1937.

Lyon states that postgraduate extension courses in pediatrics should be planned primarily to present instruction in the protection of child health, as well as in clinical pediatrics, to physicians in remote rural districts. Courses may be conducted according to the North Carolina, or circuit, plan or according to the residence plan. No single plan is sure to be effective in every locality.

It is better that the instructor have a flair for informal teaching and an interest in it than that he be a person of high technical ability.

Instruction must be along lines that the physicians may be expected to carry on away from adequate laboratory or hospital facilities. Illustrative material which can be carried away is of more value than presented clinical material. Use of the pamphlets of the United States Public Health Bureau should be stressed.

After-hour periods may include: descriptions of medical participation in solving problems of public health, medical relief and school health; motion pictures; "debunking" of certain popular literature, and demonstrations of those diagnostic and therapeutic procedures in which the group indicates special interest.

It is of primary importance that the extension activity be carried on under the sponsorship of the state medical society and that special groups within the state should not take the lead therein.

SHAWKEY, Charleston, W. Va.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

JOSEPH K. CALVIN, M.D., *President*

Regular Meeting, Feb. 21, 1939

GEORGE F. MUNNS, M.D., *Secretary*

POIKILODERMOMYOSITIS IN A CHILD. DR. HEYWORTH N. SANFORD and DR. CLARK W. FINNERUD.

Including the case in this child, there are now 40 reported cases of this condition in children under 13 years of age. This boy is 6 years old, and the condition began at the age of 3 weeks. This is the earliest age at which the disease is recorded to have occurred. The patient presents the classic symptoms of cutaneous lesions, pain in the muscles, hyperpyrexia, edema and prostration. He has low grade anemia, an increased sedimentation time and increased creatinine in the urine. A new laboratory finding, a low level of the blood vitamin C, is presented. Biopsy specimens of muscle and skin show the typical inflammatory and degenerative changes. Blood cultures have been persistently negative, and large amounts of sulfanilamide have had no effect on the condition. This makes the etiologic suggestion that this is a streptococcic infection doubtful.

At the present time the child is greatly improved as a result of maintenance on a high protein diet, rich in vitamin C, and treatment with thyroid. Orthopedic measures have enabled him to walk. Although cases of this type are presumed to have a fatal outcome in a short time, it appears that they are not all hopeless.

HYPERPYREXIA FOLLOWING OPERATION FOR CLOSURE OF CLEFT LIP OR PALATE. DR. HENRY EUGENE IRISH and DR. CHARLES E. STEPAN.

This article will appear in full in a later issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN.

THE WATERHOUSE-FRIDERICHSEN SYNDROME. DR. RALPH H. KUNSTADTER.

The case of a 12 day old infant who died of acute meningococcic septicemia and bilateral adrenal apoplexy (Waterhouse-Friderichsen syndrome), diagnosed three hours prior to death, is presented, and the literature pertaining to this syndrome is discussed.

From a clinical standpoint adrenal hemorrhage may be divided into three types: (1) that which occurs at birth or early in the neonatal period, most often discovered at autopsy, (2) that which occurs in an infant or a child in whom symptoms and signs are present and (3) acute bilateral suprarenal apoplexy with fulminating septicemia, which is believed to be due in many instances to the meningococcus and which has been described by Waterhouse and Friderichsen as a unique clinical syndrome. The literature contains reports of 72 cases of the latter type, to which is added another.

It is generally agreed that the Waterhouse-Friderichsen syndrome is caused by septic infection and that the fulminating nature of the disease has been responsible in many instances for the absence or incompleteness of laboratory investigations. The only organism found in the blood repeatedly, both before and after

death, has been the meningococcus. Including the case reported in this paper, the incidence of the meningococcus as the etiologic factor is between 65 and 70 per cent.

I believe that this syndrome can be recognized before death; pathognomonic of it are the apoplectic onset with hyperpyrexia, alternating cyanosis, purpura and shock. In view of the overwhelming sepsis and the extensive destruction of both adrenals, it appears almost hopeless to accomplish any specific therapeutic measures. It has been suggested that blood transfusion, infusion of dextrose solution alone or with a physiologic solution of sodium chloride, injection of an extract of adrenal cortex and administration of circulatory stimulants might be of value. In the case reported in this paper the time was so limited that only a blood transfusion was performed before death.

Book Reviews

The Vitamins and Their Clinical Application. By Drs. W. Stepp, J. Kühnau and H. Schroeder. No price given. Pp. 173, with no illustrations. Milwaukee: The Vitamin Products Co., 1938.

The authors have discussed the various aspects of the vitamins in this complete and well condensed book. The appendix, which has the form of a brief outline, deals with the clinical aspects of the vitamins. In it are listed the apparent functions, the possible results of deficiency and the results of absence of each vitamin. A complete bibliography is included.

Quelques vérités premières (ou soi-disant telles) sur les maladies des enfants. By Robert Debré. Price, 28 francs. Pp. 96, with no illustrations. Paris: Masson & Cie, 1938.

This is a collection of observations and precepts which the author considers of fundamental importance in the diagnosis and treatment of the diseases of infancy and childhood. The topics are grouped in the usual manner, including examination of the child, hygiene, hyperthermia, digestive disturbances, alimentary regimens and the like. The precepts are valuable principally as suggestions which must be checked by the reader's experience.

Endocrine Therapy in General Practice. By Elmer L. Sevringhaus, M.D. No price given. Pp. 192, with 39 illustrations. Chicago, The Year Book Publishers, Inc., 1938.

Dr. Sevringhaus has done an excellent piece of work in condensing the present day knowledge of the endocrine glands. He has not attempted as exhaustive a study as one finds in Zondek's recently published book on endocrinology, but a good bibliography enables one to find more detailed discussions on a particular subject. For the medical student and for one wishing a general survey of the field this book has decided value.

Your Chest Should Be Flat. By S. A. Weisman, M.D. Price, $2.00. Pp. 145, with 49 illustrations. Philadelphia: J. B. Lippincott Company, 1938.

This book is an attempt to coordinate anthropometric with clinical findings. In the main it appears that the thoracic index (anteroposterior diameter divided by transverse diameter, measured at the level of the nipples) tends to decrease from birth to adult life in normal chests, whereas in asthenic persons and persons with chronic pulmonary disease the normal decrease is arrested and the chest remains deep but narrow. Although the latter type of chest appears flat, it is in reality deep. Conversely, the broad, flat chest is normal. The author also attempts to correlate the deep, narrow chest with the childhood type of tuberculous infection. So many other factors than the shape of the chest must be considered, however, that his conclusions in this respect are not impressive. The book is written as though intended for laymen rather than physicians, but it will be of interest to those who are concerned with the bodily mechanics of the chest and the correction of defects.

Directory of Pediatric Societies*

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Prof. Luigi Spolverini, Policlinico Lungo Tevere Melini 24, Rome, Italy.
Secretary: Professor Vitetti, Rome, Italy.
Place: Boston. Time: Sept. 3-5, 1940.

American Committee:
Chairman: Dr. Henry F. Hemholz, Mayo Clinic, Rochester, Minn.
Secretary: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.

Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St., W., Montreal.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

British Paediatric Association

President: Dr. Hector C. Cameron, 23 Devonshire Pl., Upper Wimpole St., London, W. 1.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Sociedad Cubana de Pediatría

President: Dr. Clemente Inclan Costa, Manrique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Vedado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

Société de Pédiatrie de Paris

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincaré, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue du Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

NATIONAL

American Medical Association, Scientific Assembly, Section on Pediatrics

Chairman: Dr. Edward Clay Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary: Dr. Albert D. Kaiser, 16 N. Goodman St., Rochester, N. Y.
Place: Hotel Chase, St. Louis. Time: May 15-19, 1939.

American Academy of Pediatrics

President: Dr. H. F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Netherland Plaza Hotel, Cincinnati. Time: Nov. 16-18, 1939.
Region I. Place: Waldorf-Astoria Hotel, New York. Time: June 1-3, 1939.
Region II. Meeting cancelled.
Region IV. Place: Hotel Leamington, Oakland, Calif. Time: April 6-8, 1939.

American Hospital Association, Children's Hospital Section

Chairman: Miss Mabel Binner, Children's Memorial Hospital, Chicago.
Secretary: Winifred Culbertson, Children's Convalescent Hospital, Cincinnati.

American Pediatric Society

President: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid St., St. Louis.
Place: Skytop Lodge, Skytop, Pa. Time: April 27-29, 1939.

Canadian Society for the Study of Diseases of Children

President: Dr. R. R. MacGregor, 142 Wellington St., Kingston, Ontario.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

Society for Pediatric Research

President: Dr. L. Emmett Holt Jr., Johns Hopkins Hospital, Baltimore.
Secretary: Dr. A. A. Weech, 3975 Broadway, New York.
Place: Skytop Lodge, Skytop, Pa. Time: April 26-27, 1939.

SECTIONAL

North Pacific Pediatric Society

President: Dr. Frederick Fischer, 407 Riverside Ave., Spokane, Wash.
Secretary: Dr. C. L. Lyons, Paulsen Medical-Dental Bldg., Spokane, Wash.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Charles E. Conrad, 209-210 Professional Bldg., Harrisburg, Va.
Secretary: Dr. Hughes Kennedy Jr., Highland Plaza Apts., Birmingham, Ala.

Intermountain Pediatric Society

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. Hyman Green, 483 Beacon St., Boston.
Secretary-Treasurer: Dr. Henry E. Gallup, 1101 Beacon St., Brookline, Mass.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

Rocky Mountain Pediatric Society

President: Dr. John Schoonover, Republic Bldg., Denver.
Secretary: Dr. F. Craig Johnson, 1850 Gilpin St., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

STATE

Alabama Pediatric Society

President: Dr. Stewart H. Welch, 1117 S. 20th St., Birmingham.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.
Place: Montgomery. Time: April 17, 1939.

Arkansas State Pediatric Association

Chairman: Dr. G. D. Murphy, 112 Peach St., El Dorado.
Secretary: Dr. Madeline M. Melson, 909 Main St., Little Rock.
Place: Hot Springs. Time: January 1939.

California State Medical Society, Section on Pediatrics

Chairman: Dr. Harold K. Faber, 2341 Clay St., San Francisco.
Secretary: Dr. Hartzel H. Ray, 23–2d Ave., San Mateo.

Florida State Pediatric Society

President: Dr. Gilbert S. Osincup, 300 E. Colonial Dr., Orlando.
Secretary: Dr. Warren W. Quillian, 227 Avenue Aragon, Coral Gables.
Place: Concurrent with state association meeting at time of convention.

Georgia Pediatric Society

President: Dr. Charles Hall Farmer, 553 Walnut St., Macon.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St., N. E., Atlanta.
Scientific Meeting—Place: Augusta. Time: Jan. 12, 1939.
Business Meeting—Place: Atlanta. Time: April 1939.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. C. V. Calvin, 144 Golden Hill St., Bridgeport.
Secretary: Dr. E. T. Wakeman, 129 Whitney Ave., New Haven.
Time: Three meetings a year.

Indiana State Pediatric Society

President: Dr. O. N. Torian, 23 E. Ohio St., Indianapolis.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Morgan J. Foster, 837 Higley Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.

Louisiana State Pediatric Society

President: Dr. Ruth Aleman, 1407 S. Carrollton Ave., New Orleans.
Secretary-Treasurer: Dr. Philip C. de Verges, 312 Audubon Bldg., New Orleans.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Paul W. Beaven, 26 S. Goodman St., Rochester.
Secretary: Dr. Leslie O. Ashton, 842 Park Ave., New York.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. John M. Higgins, 600 S. Wilbur Ave., Sayre.
Secretary: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Allan L. Richardson, 3001 W. Grand Blvd., Detroit.
Secretary: Dr. Ward L. Chadwick, 524 Medical Arts Bldg., Grand Rapids.

Mississippi State Pediatric Society

President: Dr. Guy C. Jarratt, 920 Crawford St., Vicksburg.
Secretary-Treasurer: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Place: To be designated by society. Time: Yearly.

Nebraska Pediatric Society

President: Dr. Herman M. Jahr, 1120 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. Elmer W. Bantin, 440 Aquila Court Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

North Carolina Pediatric Society

President: Dr. W. Myers Hunter, 306 N. Tryon St., Charlotte.
Secretary: Dr. J. R. Adams, 412 N. Church St., Charlotte.

Oklahoma State Pediatric Society

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Ben H. Nicholson, 301 W. 12th St., Oklahoma City.

South Carolina Pediatric Society

President: Dr. D. Lesesne Smith Jr., 187 Oakland Ave., Spartanburg.
Secretary-Treasurer: Dr. William Weston Jr., 1428 Lady St., Columbia.

Tennessee State Pediatric Society

President: Dr. William E. Van Order, 546 McCallie Ave., Chattanooga.
Secretary: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Place: Jackson. Time: April 11, 1939.

Texas Pediatric Society

President: Dr. F. O. Calaway, 3306 Fannin St., Houston.
Secretary-Treasurer: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Place: Houston. Time: May 9, 1939.

Virginia Pediatric Society

President: Dr. W. Ambrose McGee, 616 W. Grace St., Richmond.
Secretary: Dr. John M. Bishop, Medical Arts Bldg., Roanoke.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. J. L. Blanton, 207 Fairmont Ave., Fairmont.
Secretary: Dr. Theresa O. Snaith, 450 Center Ave., Weston.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. N. C. Wetzel, 2103 Adelbert Rd., Cleveland.
Secretary: Dr. Fred Rittenger, 10515 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. T. B. Verner, 170 St. George St., Toronto, Canada.
Secretary: Dr. D. V. Hutton, 170 St. George St., Toronto, Canada.

Bronx Pediatric Society

President: Dr. Samuel T. Levethan, 254 E. 184th St., Grand Concourse, New York.
Secretary: Dr. David Greene, 910 Grand Concourse, New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Benjamin Kramer, 6 Pierrepont St., Brooklyn.
Secretary: Dr. John A. Monfort, 861 Carroll St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, July, August and September.

Central New York Pediatric Club

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Thursday of April and September.

Chicago Pediatric Society

President: Dr. Joseph K. Calvin, 2376 E. 71st St., Chicago.
Secretary: Dr. George F. Munns, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Dallas Pediatric Society

President: Dr. Harold Nesbit, 1719 Pacific Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. William O'Donnell, 1553 Woodward Ave., Detroit.
Secretary: Dr. Robert Mason, 5140–2d Blvd., Detroit.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

Fulton County Medical Society, Pediatric Section (Atlanta, Ga.)

Chairman: Dr. L. H. Goldsmith, 384 Peachtree St., N. E., Atlanta.
Secretary: Dr. James P. Hanner, 384 Peachtree St., N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St., N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. James H. Park Jr., 3717 Main St., Houston, Texas.
Secretary-Treasurer: Dr. Thomas J. Donovan, 2418 Travis St., Houston, Texas.
Place: Houston Club. Time: Third Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Urban Busiek, 200 E. Pershing St., Springfield, Mo.
Secretary: Dr. Fred Speer, 2700 Parallel Ave., Kansas City, Kan.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. H. R. Cooder, 3875 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Paul M. Hamilton, 248 E. Main St., Alhambra, Calif.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd.
Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Sidney D. Kramer, 61 Eastern Parkway, Brooklyn.
Secretary: Dr. Benjamin Stoloff, 1149 Eastern Parkway, Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: Third Wednesday of each month, October to May.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. James Dobbins, 42-04 Ditmars Blvd., Long Island City, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry H. Donnally, 1612 I St., N. W., Washington, D. C.
Secretary-Treasurer: Dr. Harry A. Spigel, 2647 Connecticut Ave., N. W., Washington, D. C.
Place: Medical Society Bldg., 1718 M St., N. W. Time: 8 p. m., fourth Thursday of October, January, February, March and April.

Memphis Pediatric Society

President: Dr. Barton Etter, 376 S. Bellevue St., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

Milwaukee Pediatric Society

President: Dr. Helen Jane Zillmer, 781 N. Jefferson St., Milwaukee.
Secretary-Treasurer: Dr. Samuel E. Kohn, 425 E. Wisconsin Ave., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Philip M. Stimson, 25 Claremont Ave., New York.
Secretary: Dr. Lucy Porter Sutton, 168 E. 74th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northwestern Pediatric Society

President: Dr. Robert Rosenthal, 437 Lowry Medical Arts Bldg., St. Paul.
Secretary-Treasurer: Dr. R. E. Nutting, 205 W. 2d St., Duluth, Minn.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Oklahoma City Pediatric Society

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Time: Every month, except June, July and August.

Philadelphia Pediatric Society

President: Dr. Samuel Goldberg, 4546 N. Broad St., Philadelphia.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

Pittsburgh Pediatric Society

President: Dr. James LeRoy Foster, Highland Bldg., Pittsburgh.
Secretary-Treasurer: Dr. E. R. McClusky, 3200–5th Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate months from October to June, inclusive.

Richmond Pediatric Society

President: Dr. Emily Gardner, 1100 W. Franklin St., Richmond, Va.
Secretary-Treasurer: Dr. T. Stanley Meade, 913 Floyd Ave., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., first Thursday of each month, except July, August and September.

Rochester Pediatric Society

President: Dr. J. Merrel Parker, 11 N. Goodman St., Rochester, N. Y.
Secretary: Dr. H. C. Soule, 16 N. Goodman St., Rochester, N. Y.
Place: Arranged by program committee. Time: Second Friday of each month.

St. Louis Pediatric Society

President: Dr. Ralph L. Cook, 508 N. Grand Blvd., St. Louis.
Secretary-Treasurer: Dr. Peter G. Danis, 634 N. Grand Blvd., St. Louis.
Place: St. Louis Medical Society Bldg. Time: Third Friday of each month from September to June.

Seattle Pediatric Society

President: Dr. Jay I. Durand, 1305–4th Ave., Seattle.
Secretary: Dr. Frederick B. Joy, 1215–4th Ave., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Philip E. Rothman, 3875 Wilshire Blvd., Los Angeles.
Secretary: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Clement Smith, 1101 Beacon St., Brookline, Mass.
Secretary: Dr. D. Murray Cowie, University of Michigan, Ann Arbor, Mich.
Place: Horace H. Rackham Graduate School, Ann Arbor, Mich. Time: Nov. 11-12, 1938.

Westchester County Medical Society, Pediatric Section (New York)

President: Dr. Norman Survis, 650 Main St., New Rochelle.
Secretary-Treasurer: Dr. Elvira Ostlund, 131 Purchase St., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.